THE

AMERICAN JOURNAL

OF THE MEDICAL SCIENCES.

JUNE, 1910.

ORIGINAL ARTICLES.

THE TREATMENT OF INTESTINAL INDIGESTION IN CHILDREN ON THE BASIS OF THE EXAMINATION OF THE STOOLS AND CALORIC VALUES.[1]

By John Lovett Morse, A.M., M.D.,

ASSISTANT PROFESSOR OF PEDIATRICS IN THE HARVARD MEDICAL SCHOOL; ASSOCIATE VISITING PHYSICIAN TO THE CHILDREN'S AND INFANTS' HOSPITALS, BOSTON.

AND

Fritz B. Talbot, M.D.,

ASSISTANT VISITING PHYSICIAN AT THE BOSTON FLOATING HOSPITAL, AND TO THE HOSPITAL OF THE MASSACHUSETTS INFANTS' ASYLUM, BOSTON.

Although a great deal has been written about the importance of the examination of the stools and the caloric estimation of the food in the feeding of infants during the last few years, especially in Germany, and considerable attention has been devoted to these points in the treatment of the digestive disorders of adults all over the world, but little has been done along these lines in relation to the feeding and treatment of the disturbances of digestion in children. There is, in the first place, very little available data as to the caloric needs of children of various ages or as to their metabolism. It is apparently taken for granted that the metabolism of children is essentially the same as that of adults. It is generally believed that young children require a relatively large proportion of carbohydrates in their food and that, as they must not only replace old but also build new tissues, they need proportionately more proteins than adults. None of these points has, however, so far as we know, been scientifically proved.

[1] Read at a meeting of the Pediatric Section of the New York Academy of Medicine, December 9, 1909.

It seemed to us that, if the stools of children suffering from disturbance of digestion, especially of the intestinal type, were examined in order to determine what contituents of the food were not being utilized and the diet regulated on the basis of these findings, due regard being paid to the caloric needs, much better results could be obtained than by the usual empirical methods. Our experience in the treatment of such cases along these lines leads us to believe that these suppositions were well founded. Our experience also leads us to believe that in most instances it is not necessary to make use of complicated methods of examination of the stools, but that comparatively simple tests, such as any practitioner can easily and quickly perform, are sufficient to give results accurate enough to form the basis for satisfactory treatment. We have also found that, with a little practice, it is a very simple matter to calculate the caloric value of the food and to regulate the proportions of fat, carbohydrates, and proteins. Strange as it may seem, we have also found that it is easier to control the diet of the child than that of an adult, and that it is at least as easy to get the coöperation of a child in carrying out the diet as it is to get that of an adult.

CALORIC NEEDS OF CHILDREN. Before taking up the treatment of these cases it will perhaps be well to sum up what we know as to the caloric needs of children, to consider the caloric value and composition of the various articles which make up the diet of the average child, and to state briefly the methods employed in the examination of the stools.

There is, as already stated, very little data as to the caloric or protein needs of children. The most valuable observations are those of Camerer,[2] which are based on a prolonged study of his own children. Czerny and Keller have collected and analyzed all the literature on this subject up to 1906 in their work on *The Nutrition of the Child*,[3] while Selter has also summarized it in a recent article on "Functional Disturbances of the Digestive Tract in Childhood."[4] The figures of these observers vary pretty widely as to the caloric needs of children. It is probably not far from the truth, however, to say that the average child of four years needs, in round numbers, about 1200 calories, or 70 calories per kilo, in twenty-four hours; the average child of eight years, 1400 calories, or 60 calories per kilo in twenty-four hours; and the average child of twelve years, 1600 calories, or 50 calories per kilo in twenty-four hours. These facts are perhaps shown better in the following table:

Age.	Total caloric need.	Calories per kilo.
4 years	1200	70
8 years	1400	60
12 years	1600	50

[2] Stoffwechsel des Kindes. Tübingen, 1896.
[3] Die Kindes Ernähung, etc., 1906.
[4] Archiv. f. Kinderheilkunde, 1906, li, 54.

The data as to the protein needs of children differ even more widely than do those as to the total caloric needs. The following table, showing in round numbers the average protein need for twenty-four hours at various ages, is probably approximately correct.

Age.	Total protein need.	Protein need per kilo.
4 years.	55 grams	3.5 grams
8 years.	60 grams	3.0 grams
12 years.	75 grams	2.5 grams

The subtraction of 5 grams from these average figures for the daily protein need in the case of girls and the addition of 5 grams in the case of active boys will make them more nearly correct. It must be remembered that these figures are for the average protein need, and not for the minimum protein need, which is, roughly, about two-thirds the average. In disturbances of protein digestion and in instances in which it is difficult to get children to take food, it is probably safe, therefore, to give only two-thirds of the above amounts, even for considerable periods of time. At any rate, there is no objection to giving much larger amounts of proteins in order to meet the caloric needs when there are disturbances in the digestion of the fats or carbohydrates. On general principles, however, it is wiser to keep the proteins down somewhere near the average need, because the metabolism of the proteins requires more energy and the products of protein metabolism are more difficult of elimination than are those of the fats and carbohydrates. An excess of proteins, therefore, requires an unnecessary expenditure of energy and is consequently not economical. While proteins may be used as substitutes for fats and carbohydrates, they cannot, of course, be used as substitutes for proteins beyond a certain point, that is, the minimum protein need. Within reasonable limits variations in the relative amounts of fats and carbohydrates in the diet probably make no difference to the average well child, the relative amounts taken depending largely on the habits and tastes of the community, of the special family, and of the individual child. In disturbances of digestion fat may be substituted for carbohydrates and carbohydrates for fat with great advantage, provided the total caloric value of the food is kept up. The fats may be entirely replaced by carbohydrates over considerable periods without doing any harm. There is a certain amount of risk in replacing the carbodydrates entirely by fats, however, because of the danger of developing acid intoxication. In the treatment of disturbances of digestion in childhood this procedure is, however, seldom, if ever, necessary.

Caloric Value of Foods. We have compiled the following table giving the caloric value and composition of the various foods commonly given to children suffering from disturbances of digestion. These figures, while not absolutely accurate are, we believe, accurate enough for practical purposes. It has seemed to us sufficiently

accurate and certainly much more simple and practical to calculate the food values of ordinary helpings of cooked food rather than of weighed portions or of uncooked foods. We have found it very easy to determine from this table not only the caloric value of the child's food but also the amounts of proteins, fats, and carbohydrates. With it we have also found it very easy to plan out a diet for a child to give not only the proper number of calories, but also the desired relations between the different food elements.

TABLE OF FOOD VALUES.

	Calories.	Grams. F.	C.	P.
Whole milk, 1 quart	670	38	43	34
Skimmed milk, 1 quart	400	10	43	35
Gravity cream, 1 pint	860	77	22	14
Buttermilk, 1 quart	360	5	43	35
Whey, 1 quart	260	5	43	9
Beef juice, 1 ounce	10	..	..	2
Crackers, 1 ounce[5]	120	3	20	3
Bread, 1 slice[6]	75	0.5	15	3
Zwieback, 1 slice[7]	120	3	20	3
Shredded wheat biscuit	105	0.5	22	3
Oatmeal and other cereals (cooked), 1 tablespoonful	25	..	5.5	1
Rice (cooked), 1 tablespoonful	45	..	10	1
Potato, size of large egg	100	..	20	2
Macaroni (cooked), 1 tablespoonful	30	0.5	5	1
Egg (whole)	72	5	..	7
Egg (yolk)	60	5	..	4
Egg (white)	12	..	..	3
Meat, fish (cooked), 1 ounce[8]	60	3	..	7
Butter, 1¼ inches cube = 1 ounce	225	24	..	..
Olive oil, 1 tablespoonful	125	14	..	..
Sugar (cane), 1 rounded teaspoonful	25	..	6	..
Sugar (milk), 1 rounded tablespoonful	60	..	15	..
Green peas (cooked), 1 tablespoonful	40	..	7	3
Carrots, squash, turnip (cooked), 1 tablespoonful	30	..	6	1
Orange (medium sized)	50	..	13	..
Apple (medium sized)	70	..	17	..

Clear soups and broths made without rice or barley have practically no nutritive value. The nutritive value of the "fodder" vegetables—such as spinach, string beans, asparagus, lettuce, tomatoes, and cucumbers—is so slight that it may be disregarded.

CHARACTERISTICS OF THE CHILD'S STOOL. Before taking up the methods used in the examination of the stools it may be well to summarize in a very general way some of the characteristics of the child's stool. This is normally homogeneous in consistency. Lumpy and mushy stools are pathological. The former are found when

[5] Crackers vary so much in size that they must be weighed to determine how many it takes to weigh an ounce.

[6] Bread—a slice = 4 inches square and three-eighths inch thick = 1 ounce.

[7] Zwieback—1 slice = large slice.

[8] The lean of a lamb chop weighs about an ounce; so does a piece of meat about 1¼ inches cube.

there is an excess of milk, meat, or eggs in the diet or when the child is underfed; the latter when there is an excess of foods which have a considerable indigestible residue, such as coarse bread, fruit, and vegetables. Large masses of undigested food are usually the result of improper mastication. The reaction to litmus paper is weakly alkaline, weakly amphoteric, or neutral. A very strong alkaline reaction, especially if accompanied by a putrefactive odor, suggests protein putrefaction. A strong acid reaction, associated with a rancid odor, suggests disturbance in the digestion of fat; if associated with the odor of lactic or acetic acid, disturbance in the digestion of carbohydrates. The movement is often frothy or shows bubbles here and there in the latter condition. Microscopic examination shows a few remains of a vegetable nature, single yellow masses, supposed to be albuminous remains, a few muscle fibers, a few crystals, rare starch granules, and microbes which may stain blue with Lugol's solution. The background is granular and made up of the bodies of bacteria and intestinal secretions. When acetic acid is added, a few drops of fatty acid are seen in each field after heating.

Types of Pathological Stools. Several of the types of pathological stools are characteristic enough to deserve special mention; these are the fatty stools, the stools of carbohydrate indigestion, and the catarrhal stools.

The *fatty stools* are gray or white in color, dry or of clay-like or creamy consistency, acid in reaction, and of a rancid odor. Microscopically they show a large excess of fat in various forms.

The *carbohydrate stools* are brown or golden-yellow in color, salve-like in consistency, acid in reaction, acid or sour in odor. Microscopically they show undigested starch and often an excess of Gram-positive bacteria. If the examination is hasty they may often be mistaken for normal stools.

The *catarrhal stools* show an excess of mucus both macroscopically and microscopically. The stool may be almost entirely composed of mucus or the mucus may be distributed through it. It is often associated with protein putrefaction and a foul odor.

Types less frequently met are those in which there are a large excess of undigested muscle or connective-tissue fibers. Mixed forms are more common than the pure types and more different to interpret.[9]

Methods of Examination. The methods employed in the examination of the stools in our cases were as follows: The child's diet, especially in the early years, is almost always a simple one in comparison with that of the adult and in most instances resembles so closely the test diets recommended by Selter and Schmidt that it is possible to draw the same conclusions from the examinations of

[9] A detailed description of the various types of stools can be found in Selter's article in the Archiv f. Kinderheilkunde, 1909, li, 54.

the stools as when the test diets are given. Test diets were, therefore, not used in any of our patients. The character and the quantity of the food taken in the preceding twenty-four or forty-eight hours was known in every instance, however, so that for all practical purposes the children had had a test diet.

During the past two years one of us (Talbot) has controlled the results of the microscopic examination of the stools by numerous quantitive chemical examinations and has found that a very accurate estimate of the amount of fat and protein in the stool can be obtained by a simple microscopic examination. In most instances, therefore, no quantitative chemical analyses were made. No attempt was made to verify the microscopic findings as to starch by chemical examination, it being taken for granted, that, if there was no excess of starch under the microscope, it was properly digested. This conclusion is probably correct enough for every-day clinical work, although there is no doubt that starch may be present in the stools when it cannot be detected by the microscope.[10] The methods followed were essentially those described by Schmidt.[11]

Macroscopic Examination. The form, coherency, consistency, color, and odor, and the presence or absence of extraneous matters such as pus, blood, mucus, parasites and curds, are noted. If the stool is homogeneous only one part is tested with litmus paper for the reaction. If the stool varies in composition the reaction is tried in several portions. This is done by placing two moistened pieces of litmus paper (red and blue) upon (not in) a fresh surface of the stool.

Microscopic Examination. The microscopic portions are examined first with a low power objective and later with a No. 7 objective to bring out the detailed structure. If the feces are hard they are first rubbed up with a little water, otherwise they are thoroughly mixed and three small portions are placed on a slide. The first is crushed out very thin under the cover glass and examined in the fresh condition. Another is stained with Lugol's solution (iodine, 2; potassium iodide, 4; distilled water, 100) and examined under the cover glass for starch. The third is stained with a saturated alcohol solution of Sudan III.

In the first specimen any excess of undigested muscle fibre, connective tissue, or vegetable fibers can be studied, and pathological elements, such as blood, pus, and eggs of parasites, differentiated. A preliminary estimation of the amount of neutral fat, fatty acids, soaps, and starches can also be made. Under the cover glass the starch granules will stain blue or violet and certain microbes will stain blue. There are practically no unchanged starch granules

[10] Rosenheim, Pflüger's Archiv., xlvi, 428; Strassburger, Deuts. Archiv. f. klin. Med., lxi, 590.

[11] The Test Diet in Intestinal Diseases.

in a normal stool. An excess is always pathological. (It is important to remember in this connection that almost all baby powders contain starch. Their presence, therefore, must be ruled out.) Iodophilic bacteria, or those which stain blue with Lugol's solution, are suggestive of an early disturbance in the digestion of starch. Under the third cover glass neutral fat drops and fatty acid crystals stain red. Soap crystals do not stain with Sudan III. After this cover glass is examined and the microscopic picture is clear, a drop of glacial acetic acid is allowed to run under the cover glass, is thoroughly mixed in, and then heated until it begins to boil. This process turns the soaps into neutral fat and fatty acids, which, while warm, appear as large, red, stained drops, and upon cooling crystallize. They usually retain the red stain. Any increase in the amount of fat after the addition of acetic acid indicates the presence of a corresponding amount of soaps. An excess of neutral fat indicates that the digestion of fat is not carried on normally, and an excess of fatty acids and soaps that the digestion is normal but assimilation is abnormal.

Illustrative Cases. In a not inconsiderable number of instances the difficulty in digestion is due more to an excess in the quantity of food than to errors in the quality. The following case is an example:

Case I.—A boy, aged four and one-half years, was on a very carefully regulated diet. He was, nevertheless, having from five to six large, loose movements, macroscopically digested, daily, and was losing in weight. He had an enormous appetite and his mother had allowed him to eat as much as he wanted, although she had been careful not to give him anything outside of the prescribed diet. It was found that the caloric value of his food was nearly twice as great as was necessary. The quantity as well as the quality of his food was then regulated so that he got only a little more than enough to cover his caloric needs. The number of movements immediately dropped to two a day and he began to increase in weight.

It is very easy, in attempting to regulate the diet to the child's digestive capacity, to err on the other side and give an insufficient amount of food. It is also very easy, if the stools are not examined, to make up one's mind that a patient cannot digest certain food elements, and hence to cut them out of the diet unnecessarily. The following case is an example of both of these mistakes:

Case II.—A girl, aged five and one-half years, that had been treated for chronic intestinal indigestion by another physician for the preceeding six months, came into our hands. During that time she had been taking only modified milk and a little meat. It was said that she could not digest starch. She was having two movements daily, which were said to be foul and to contain mucus. She had not gained in weight for a year. It was found on calculation that the caloric value of her food was somewhat below the normal

and that it contained a large excess of proteins. Measured amounts of bread, cracker, and butter were immediately added to her diet. Examination of the stools a few days later showed that she was digesting the starches as well as the fats and proteins. The amount of starch in the diet was rapidly increased and the modified milk replaced by whole milk, the caloric value of the food being increased to meet her needs. She began to gain in weight at once, gaining four pounds in the first month. Further study showed that she was able to digest all the food elements normally and to eat an ordinary, reasonable diet for her age. The mucus quickly disappeared from her movements on the more liberal diet. The advantages of the calculation of the caloric value of the food and of the examination of the stools in this instance are self-evident.

In many, or perhaps most, instances it is not so much the total caloric value of the food that is at fault as an improper balance of the different food constituents. In such instances there is usually a large excess of some one element. The following cases are examples:

CASE III.—A boy, aged two years, had been losing color and weight for about three months. He was not as vigorous as in the past, but did not seem really sick. He had not vomited, but had had two movements daily, which the mother said seemed normal in every way. She thought that he had not been eating enough, and in order to fatten him had given him a rich Jersey milk with extra cream. The mother, being a Southerner, had also given him corn bread and bacon. Analysis of his diet showed that he was getting 1200 calories per day, while his caloric needs were approximately only 1000 calories per day. His apparent loss of appetite was presumably due to the excessive richness of his food. He was rather thin and flabby and somewhat pale. Otherwise the physical examination showed nothing abnormal. He was given a reasonable diet. The cream, corn bread, and bacon were stopped and the milk changed from Jersey to Holstein. He gained a pound on this diet in the next two weeks, but did not improve as much in his general condition as his mother thought he should. His case was therefore gone into more carefully.

His diet March 1 consisted of milk, 34 ounces; cereal, 4 tablespoonfuls; beef juice, 2 tablespoonfuls; bread, three slices, and a baked potato. This gives a total of about 1150 calories and contains, in round numbers, 40 grams of fat, 130 grams of carbohydrates, and 50 grams of proteins. He had two movements during the twenty-four hours. The second one was small, yellow, semisolid, of foul odor and alkaline reaction, and contained a small amount of mucus. Microscopically it showed considerable undigested starch and many iodophilic bacteria. There was no undigested neutral fat or fatty acid, but a moderate excess of soap and a small amount of mucus.

On the basis of these findings the amount of starchy food was cut down and meat added to his dietary. His diet March 8 was made

up as follows: Milk, 33 ounces; cereal, 2 tablespoonfuls; bread, two slices; a baked potato, and two small slices of chicken. This gives about 1050 calories and contains, in round numbers, about 40 grams of fat, 105 grams of carbohydrates, and 50 grams of proteins. His movement was brown, soft, of uniform consistency, alkaline in reaction, and contained a very small amount of mucus. Microscopically it showed a slight excess of neutral fat and fatty acids, but no excess of soaps or meat fibers. There was no undigested starch. The amount of milk was then cut down and that of the starch slightly increased. From this time on the improvement was steady and uneventful.

CASE IV.—A boy, aged two and one-half years, was brought because of a large abdomen which had been steadily increasing in size for about six months subsequent to a rather severe attack of diarrhœa. Tubercular peritonitis had been suspected. His appetite was always good, often enormous, occasionally capricious. There was no nausea or vomiting and only a moderate amount of flatulence. The bowels moved two or three times daily, the movements being very large, but soft. On passage they were like strips of tape, but on standing formed a homogeneous mass. He had lost considerable weight and on that account was being given rich milk, extra cream, and a great deal of butter. His parents were about to begin cod liver oil also. He was unable to get about much because of the large size of the abdomen. He did not complain of pain and had never been jaundiced.

He was considerably emaciated and moderately pale. His tongue was nearly clean. The liver and spleen were not palpable. The abdomen was very large. The circumference of the chest at the nipples was 49 cm.; that of the abdomen at the costal border, 59.5 cm.; and that at the navel, 56 cm. There was no dulness in the flanks, no fluid wave, no muscular spasm and no tumor.

His movement was very large, unformed, of uniform consistency, soft and spongy, white, with a slightly yellowish tinge. The odor was foul, the reaction alkaline. There was a small amount of mucus intermixed. Under the microscope practically the whole field was made up of soap splinters. There was rarely a neutral fat drop, but no fatty acids or calcium soap. There was very little mucus, no meat fibers or undigested starch. Gram-decolorizing bacteria predominated. There was an occasional large "blue bacillus" and many Gram-staining bipolar bacilli and cocci, but no bifid bacilli.

In this case the chronic duodenal indigestion and the consequent weakening of the power of assimilating fat had been entirely overlooked because of the general emaciation and the enlargement of the abdomen, and the worst possible form of diet prescribed. One familiar with the condition would undoubtedly have been able to

make the diagnosis without the microscopic examination of the stool. It, nevertheless, furnished important corroborative evidence.

Sometimes the microscopic examination of the stools will give warning of impending trouble several days before the appearance of any symptoms or macroscopic changes in the movements. In fact, the movements may appear normal even when there is a considerable excess of fat in the form of soap. The following case is an example:

CASE V.—A girl, aged two years, had been running down for some time, and had grown steadily worse on the diets prescribed by several physicians, all of which had contained a large amount of fat. The examination of the stools had disclosed the cause of the trouble and she was doing very well on a diet almost free from fat. After a time it was thought wise to try to work fat into the diet again. Two ounces of each ten ounces of skimmed milk was, therefore, replaced by whole milk on September 12. The mother reported September 16 that the little girl was doing well in every way. The movement, which macroscopically was perfectly normal, showed under the microscope a considerable excess of fat. The mother found the child out of sorts on her return home, irritable, the appetite poor, and the movements undigested. It was several days after the whole milk was stopped before she was right again and the stools normal.

The finding of vegetable and fruit fibers in excess, both microscopically and macroscopically, is not uncommon and explains a good many cases in which the movements are too frequent and too large in amount. It also explains a certain number of cases of constipation.

It would be very easy to detail many other cases illustrating the same and similar points, but it seems to us that those given are sufficient to demonstrate the advantages of the regulation of the diet in the intestinal indigestion of children on the basis of the findings in the stools and the caloric values of foods over the old "hit or miss" methods.

THE TREATMENT OF HEMORRHAGE FROM GASTRIC ULCER.

WITH SPECIAL REFERENCE TO GASTRIC LAVAGE.

BY J. KAUFMANN, M.D.,

PROFESSOR OF CLINICAL MEDICINE IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY; ATTENDING PHYSICIAN TO THE GERMAN HOSPITAL, NEW YORK.

WHENEVER severe hemorrhage occurs in gastric ulcer it not only frightens the patient, but often enough the physician as well. The physician, however, should not forget that fatal bleeding from gastric ulcer is comparatively rare, as is seen from the statistics of

men who personally have followed a large series of ulcer cases. Fenwick[1] states that death due to uncontrollable hemorrhage has occurred in 3.4 per cent. of his cases; von Leube[2] gives his proportion as 1 per cent.; Jacoby[3] also gives 1 per cent.; while Ewald[4] claims that with his large experience he has never seen a fatal issue caused directly by profuse hemorrhage. A number of other authors[5] figure between 3 and 5 per cent., so that we may put the average at about or below 3 per cent.

We do well to keep these facts in mind, particularly when confronted with hemorrhage of a severe type. With moderate hemorrhages the immediate danger to life is not great, although they may become dangerous when often repeated, thereby gradually undermining the vitality of the patient. The frequent occurrence of small or moderate hemorrhages may call for surgical treatment in order to prevent further bleedings and to arrest the development of cachexia which often follows the frequent loss of blood. I must abstain, however, from discussing this specific indication, since it is the principal object of this paper to deal with the *direct* treatment of active bleeding. I only wanted to point out that repeated hemorrhage of moderate severity, although for the time being not dangerous to life, may prove much more dangerous for the final outcome than those alarming excessive hemorrhages.

With spontaneous and very profuse bleeding, the severe anemia resulting from the sudden great loss of blood brings about changes in the system, which if undisturbed, of themselves tend to arrest the bleeding. The vasoconstriction which goes with the advent of sudden anemia and with syncope allows the bleeding vessel to contract, and the low activity of the heart, permit the formation of a thrombus.[6] The formation of a thrombus is particularly necessary in those cases of chronic ulcer "where the eroded artery lies like a rigid pipe in the fibrous wall of the ulcer, and being unable to contract, can only become occluded by the process of clotting" (Fenwick, p. 135). When the clotting is not quickly and efficiently accomplished, such patients may bleed to death very rapidly. A postmortem examination may show that the ulcer after penetrating through the whole gastric wall had eroded a larger branch of the arteria pancreatica or lienalis, or one of the main arteries itself. The finding of the anatomical conditions demonstrates that probably no medical treatment could have checked the bleeding and on

[1] Ulcer of the Stomach, p. 199.

[2] Verhandlung. der Gesellsch. f. Chirurgie, 1897.

[3] Congr. Amer. Phys. and Surg., Med. Record, 1897.

[4] Deutsche Klinik, v, 508.

[5] For further statistics: see Lieblein, Deutsche Chirurgie, xlvi, 100, and Bamberger, Die Behandlung des chron. Magengeschwürs Verl., Julius Springer, 1909, 24.

[6] Von den Velden (Arch. f. exp. Path. u. Pharm., 1909, lxi, 37), lately demonstrated that after each hemorrhage the influx of serum from the tissues into the blood carries with it a great deal of thrombokinase, a substance which is present in all tissues and greatly increases the coagulability of the blood

the other hand leaves it often very doubtful whether surgery could have accomplished it.

Owing to the rapid course in most of these cases we usually find the patient so exsanguinated that the result of an operation becomes very problematical, especially when we consider the great difficulties that are often met with even postmortem in trying to locate the bleeding. We must remember that excessive bleeding not only originates from eroded arteries at the base of the ulcer, but also from ruptured veins around the ulcer, or from minute erosions at distant points, so that even resection of the ulcer may fail to remove the source of the bleeding. Without denying the possibility of checking the bleeding by surgical means, the conditions present are as a rule unfavorable for a successful operation. We must therefore console ourselves to the fact that a certain number of cases are lost, no matter what treatment we may try. Luckily these cases are not frequent, as we learned from the small total percentage of fatal hemorrhages already stated.

In dealing with excessive hemorrhage we should not be influenced too much by such experiences. We do far better to base our plan of treatment on the knowledge of what actually happens when the bleeding comes to a standstill. As we have argued before, it is either vasoconstriction or the forming of a thrombus which brings about hemostasis, both processes developing with the effect of anemia and of the weakened action of the heart. Nothing seems therefore more out of place than the routine treatment usually met with, which directs all efforts toward overcoming the depressed condition of the circulation. Yet from a large experience I can state, that the attempt to strengthen the weakened heart by administering heart tonics, infusions of salt solutions, etc, is greatly overdone by most physicians; as a rule it dominates the whole plan of treatment and not infrequently is the only treatment instigated. When the desired effect of energetic stimulation has been reached, the vigorous action of the heart will eventually result in freeing a freshly formed thrombus and thus cause a renewal of the bleeding. Since the continuation of the bleeding forms the main danger of such situations, it is obvious that energetic stimulation may increase the danger by bringing about exactly what we should try to prevent. For this reason it must be considered unwise to resort indiscriminately to vigorous stimulation.

We are all the more justified in abstaining from energetic stimulation, as general experience teaches that most cases with profuse hemorrhage, when not ending fatally on account of uncontrollable bleeding, overcome anemia and disturbance of circulation surprisingly well. It may sound paradoxical, yet it is a fact that just such cases of chronic ulcer, which at one time or other had a very profuse hemorrhage, give the best end results both in regard to the palliative and the curative treatment of the ulcer.

As an illustration I briefly give the history of a woman who after suffering for several years from chronic ulcer, at the age of thirty-six, went through an extremely severe gastric hemorrhage. She was so exsanguinated and presented such marked evidence of progressive heart failure, that Dr. F. Lange, who saw the patient with me, declared her moribund. Nevertheless during the spell of great weakness the bleeding stopped and the patient gradually recovered from this apparently hopeless condition. After a long continued dietetic treatment, while increasing both in weight and strength, she lost all symptoms of gastric ulcer and has since then (over ten years now), remained perfectly well. I could mention a number of similar instances which show that anemia and weakness of the heart may prove helpful in bringing about cessation of the hemorrhage and in the majority of cases are well tolerated, provided the bleeding stops.

A former generation of physicians who were familiar with the effects of venesection realized the importance of such observations. When confronted with uncontrollable hemorrhage, they would perform a venesection, expecting to have the bleeding stopped by the resulting syncope and its effect upon the circulation. When the venesection is performed according to the rules given by Marshall Hall, with the patient sitting upright and a quick flow of the blood is secured, it leads more easily to syncope and thereby eventually to the control of the internal hemorrhage. I saw Kussmaul successfully carry out this principle in a case of extreme hemoptysis, in which the patient within a short time lost enormous quantities of blood. All accessible methods of hemostasis were tried in quick succession without result, when finally a full venesection caused syncope and with it brought the bleeding to a standstill. We find the same principle in another method, which, less heroic than venesection, tries to imitate its effect by applying elastic ligatures to the four extremities. As a result a great quantity of blood accumulates in the limbs and the internal organs become anemic. This method was also successfully employed in cases of severe gastric hemorrhage. I have discussed this question somewhat fully because I have often been impressed by the great activity of physicians in making stimulation the most important part in the treatment of excessive hemorrhage. We should be very reluctant with stimulation, employing it only in case of stern necessity and even then cautiously and judiciously. The paramount issue of the situation is the stoppage of the bleeding and this, as we have seen, is better safeguarded by avoiding stimulation.

As soon as the bleeding has come to a standstill, our efforts should be directed principally toward preventing a recurrence of the bleeding. This is best accomplished by securing complete mental and bodily rest. The patient should be kept upon his back with an icebag on the epigastrium to control the movements of the stomach. A full

dose of morphine helps here more than anything else and at the same time makes it easier for the patient to stand the fasting of the following days. It is essential to give the stomach absolute rest by abstaining from all nourishment. I find it better even to omit rectal feeding during the first few days, because nourishing enemas often provoke peristalsis of the stomach and are known to stimulate gastric secretion (Umber).[7] We must be aware that with any functional activity of the stomach a thrombus might easily be dislodged or dissolved. The danger arising from such an accident is certainly greater than the danger of starvation, providing the fasting is not injudiciously continued for too long a period. During the last few years the Lenhartz treatment has induced physicians to discontinue the traditional starvation period and to feed their patients immediately after the hemorrhage.

The lively discussion which followed Lenhartz's recommendation has certainly demonstrated the fallacy of continuing the starvation period not only for days but for weeks, as has been done. On the other hand it made clear that the views upon which Lenhartz bases his advice are erroneous in some respects. We are here only concerned about the effect of early feeding on a bleeding ulcer. Reports are becoming more numerous that early feeding, according to Lenhartz, caused recurrence of the hemorrhage, thus violating the most important indication, that of preventing a continuation of the bleeding. It is possible that further observations will teach us to single out certain conditions, in which early feeding may be permissible. For a general rule, however, it is safer to adhere to the old principle of having the patient fast a few days after the hemorrhage. How many days and, further, how carefully to feed afterward, should be decided in each individual case.

When the hemorhage does not stop, the question arises, "What can we do to check the bleeding?" Of the many remedies employed for this purpose, I can only discuss shortly some of the more important ones. Formerly styptics were used a great deal—acetate of lead, perchloride of iron, oil of turpentine, etc. As hemostatics they are very unreliable, while on the other hand they are apt to increase the ever present and annoying nausea and often excite vomiting. The same can be said for the internal use of more modern preparations like ergot. Neither have I ever seen any benefit from ergot preparations given hypodermatically. Calcium chloride in full doses may prove of value in cases in which the bleeding is continuous but slight in amount, but it is slow in its action and will hardly exert any influence in profuse bleeding. Adrenalin has the great disadvantage that the vasoconstriction produced by this drug is followed by a period of vasodilatation, which may eventually cause a renewal of the hemorrhage. As for the results derived from gelatin pre-

[7] Berl. klin. Woch., 1905, No. 3.

parations given per os or per clysma, the reports are as yet very doubtful, and when given subcutaneously it may cause tetanus, unless the preparation is absolutely reliable. As several days are required to obtain a freshly sterilized preparation, it is likely to arrive too late,

Very promising seems the employment of serum, which has recently been introduced for the treatment of hemophilia. So far I only once had occasion to observe the administration of diphtheria serum in a case of fatal gastric bleeding, from a ruptured varicose vein. The case was so peculiar that it allows no opinion as to the effect of the serum. The same patient also received escalin (aluminium-glycerin paste), which is highly praised by Klemperer;[8] others counsel against its use on account of the bad results which they observed.

The most reliable of the internal remedies is bismuth, which is largely used in the treatment of gastric ulcer since Kussmaul and Fleiner's recommendation. The crystalline bismuth subnitrate is preferable because, as Matthes[9] has shown, this salt sticks to the surface of the ulcer, accumulates there and thus makes a protective coating for the ulcer.

Naunyn[10] reports a case, in which lavage of the stomach followed by the administration of bismuth stopped a profuse gastric hemorrhage. The patient who at the same time suffered from excessive diarrhœa, died from exhaustion and severe anemia. She had received 20 grams of bismuth subnitrate thirty-six hours before death and twenty-four hours later an additional 5 grams. Autopsy showed that the ulcer was filled by a clump of bismuth about 20 grams in weight, while the remainder of the stomach contained but a very small quantity. Naunyn's experience demonstrates that we may expect a more efficient action of bismuth when the stomach is previously emptied by lavage.

This leads me to the discussion of the method, which I consider of greatest importance in the control of gastric hemorrhage, namely gastric lavage. Since I first saw lavage performed in cases of bleeding ulcer at Kussmaul's clinic more than twenty-five years ago, I have employed this treatment in a series of cases of profuse hemorrhage, in almost every case with favorable result. I have no hesitation therefore in recommending gastric lavage as the most expedient means in the treatment of severe hemorrhage, provided it is carefully applied.

As I am well acquainted with the aversion which most physicians harbor against this procedure, I shall discuss the pros and cons in detail. The most frequent objection raised against lavage is that it may cause perforation. Perforation, however, only takes place

[8] Therapie der Gegenwart, 1907; Jacobson, Therapie der Gegenwart, 1909.
[9] Centralbl. f. innere Med., 1894.
[10] Deutsch. med. Woch., 1898; Vereinsbeilage, No. 3.

after the ulcer has penetrated the different layers of the stomach and has led to necrosis of the serosa. This is evident when we examine the anatomical features of the opening. As a rule the opening is small and circular, showing the defect produced by necrosis. I have found this condition in a case that I reported,[11] in which perforation set in one hour after the stomach was washed in order to prepare the patient for the previously planned gastroenterostomy. The same condition was found in similar cases. To my knowledge nobody has ever reported that the perforation opening was a lacerated tear through non-necrotic tissue, a finding which would prove that the perforation was a direct result of lavage. This, too, could only occur by forcibly overdistending the stomach by great quantities of water, a possibility which we may well ignore, if ordinary precautions are observed. With a carefully performed lavage the danger of causing perforation by overdistention, is out of the question. On the contrary, lavage exerts its greatest benefit by doing away with the real cause of overdistention, by removing the large quantities of accumulated blood, acid secretions, food remnants, and gas, which are usually present in such cases, often producing an enormous distention of the stomach. We can therefore dismiss the objection that gastric lavage may cause perforation. If it should happen incidentally, that lavage is undertaken just before the threatening perforation actually occurs, the cleaning of the stomach will prove very beneficial in preventing the escape of stomach contents through the perforation, thereby greatly improving the prognosis. In my case cited before, the good result obtained by resecting the perforated ulcer must to a great extent be credited to this fact. It is well known that the prognosis is far better when perforation takes place at a time when the stomach is empty.

A further objection to lavage is that it disturbs the complete rest of the stomach, which as we have seen before, is essential in order firmly to secure the freshly formed thrombus. This is perfectly correct, when the hemorrhage has ceased and we may assume that an efficient thrombus has been established. However, conditions are altogether different when the bleeding continues, because then either no thrombus has developed, or if formed, does not completely fill the opening of the vessel. We know from general surgical experience that such a partially occluding thrombus is often the cause of continued bleeding. The removal of such inefficient thrombi is not only not dangerous, but on the contrary it is a necessity in order to give the bleeding vessel a chance to contract or to form a more efficient thrombus. From what I have seen this explanation holds also true for gastric hemorrhage, because I observed in several instances, that the bleeding ceased suddenly during the act of lavage. This shows how unjustified is the traditional rule handed down in

[11] Kaufmann, Amer. Jour. Med. Sci., April, 1904.

all text-books, that lavage is absolutely forbidden in gastric hemorrhage. It should certainly not be condemned in such general fashion, because lavage may prove the best procedure to stop the bleeding.

Finally comes the objection that the introduction of the tube is difficult and exciting for the patient. When lavage is given by a physician experienced in this method he will overcome the difficulties in inserting the tube, particularly when he wins the patient's confidence by his assurance. As a rule I was able to insert the tube, even with the patient lying on his back without causing excitement or great exertion. It is advisable to insert the tube just far enough to secure siphonage and to limit the quantity of water used each time to about 300 c.c.

As for the advantages of lavage, I have already mentioned the release of partially occluding thrombi. A further very striking advantage is the benefit of lavage when the stomach is distended by large quantities of contents. These stagnating masses are usually very sour and fermenting, and their presence not only causes nausea and pain, but acts very harmfully by constantly irritating the mucous membrane to intense hypersecretion, thereby further increasing the amount of gastric contents. Again, the fermentation always connected with such conditions invariably leads to pronounced and sometimes to enormous gas distention of the stomach, so that when the tube is introduced the contents shoot out under high pressure, even, as I have experienced, with an explosive sound. It seems hardly necessary to explain how detrimental such a distention is in every respect. No doubt it is frequently the direct cause of the continuation of the bleeding. The removal of the fermenting masses not only relieves annoying symptoms of gastric irritation, but eventually brings about a direct cessation of the bleeding by allowing the emptied stomach to contract and this aids in the occlusion of the eroded vessel.

The evacuation of the stomach and the contraction which follows it are of the greatest importance for the improvement of circulatory disturbances. I saw cases of gastric hemorrhage in which the pronounced symptoms of insufficiency of the heart were only in part due to anemia, but to a much greater extent they were caused by the pressure of the gas distended stomach against the diaphragm and heart. In these cases circulation was at once improved when the stomach was emptied, while the anemia remained unchanged. I had a very instructive case of this type twelve years ago: The patient was a woman, aged thirty years. After excessive gastric bleeding the pulse rose to 160, became fluttering, and the heart action was so weak and irregular, that several physicians connected with the case considered her at the point of death. The stomach was full and so distended that it almost reached the level of the axilla. After the stomach was emptied, the pulse rate immediately came down to 116, the heart action became stronger, and the patient recovered.

The understanding of such conditions has been greatly advanced by the recent study of acute gastric dilatation. The knowledge of this clinical picture is not quite as new as some writers would make us believe. At any rate acute gastric dilatation is frequently associated with gastric hemorrhage. It is generally admitted that the most rational and the most effective treatment of acute gastric dilatation is prompt evacuation by lavage. This holds true for cases of acute dilatation in connection with hemorrhage. Let us hope that this discussion will encourage physicians to resort more frequently to lavage in gastric hemorrhage than heretofore.

Of the cases of severe gastric hemorrhage which I successfully treated by lavage, I wish to report as an illustration one which is particularly interesting. The patient, aged thirty-nine years, had suffered for sixteen years from the cardialgic form of chronic ulcer without hemorrhages. In June, 1906, an abscess in the pyloric region was opened; the gall-bladder was found normal and it is probable that the abscess had formed after a perforation of the ulcer. Soon after the operation severe gastric symptoms recurred with evidence of pyloric stenosis. Since these symptoms persisted in spite of prolonged medical treatment we advised operation. In June, 1907, Dr. Willy Meyer performed a posterior retrocolic gastroenterostomy by means of sutures; at the pylorus a hard mass was found producing partial obstruction. Eight hours after the operation hematemesis set in, which in the following twenty-four hours recurred five times, causing such a very great loss of blood that the condition of the patient became very alarming. We decided to evacuate and wash the stomach. At first we obtained large quantities of dark bloody material; then the washings became bright red showing that the bleeding was still active, when suddenly the water returned clear. Before withdrawing the tube a large dose of bismuth subnitrate was poured into the stomach. The bleeding ceased and an uninterrupted convalescence was followed by a perfect cure.

In this case gastric lavage stopped an attack of severe bleeding, which followed a gastroenterostomy, an interesting fact, when we consider that surgeons advise this operation to check excessive hemorrhage. Nor is this experience anything unusual. A number of surgeons in this country and abroad have reported the occurrence of severe hemorrhage following a gastroenterostomy. I mention Mayer,[12] Busch[13] (reporting from Körte's clinic), Clairmont[14] (from von Eiselsberg's clinic), and others. Kocher,[15] in discussing his own similar experiences, confirms Clairmont's view, that the possibility of causing a hemorrhage forms one of the main dangers

[12] Bruns' Beiträge z. klin. Chirurgie, 1908, vi.
[13] Langenbeck's Archiv, xc, 1.
[14] Mittheil. aus d. Grenzgeb. d. Med. u. Chirurg., 1909, xx.
[15] Ibid.

of gastroenterostomy, because in certain cases this operation not only fails to stop bleeding, but on the contrary it may be the direct cause of its occurrence. Kocher therefore advises more radical operations like excision of the ulcer, etc., whenever possible.

It is not my intention to enter here into a discussion of the difficult and as yet unsettled question of surgical treatment for gastric ulcer. I only wish to emphasize that in contemplating operative measures we should distinguish more clearly between operations performed for the purpose of perfecting a final and complete cure of the ulcer and those operations which are undertaken for the immediate control of hemorrhages. I have already discussed the advisability of radical operations in cases in which the ulcer, not yielding to medical treatment, causes frequent hemorrhages, and thereby greatly undermines the vitality of the patient. In such cases, however, it is decidedly better not to operate at the time of acute bleeding. Here the purpose of the operation is not to check a given hemorrhage, but to prevent the occurrence of bleedings. The radical operation necessary to accomplish this, certainly promises better results when performed after the patient has recovered from a hemorrhage. On the other hand, when an operation is undertaken for the very purpose of checking the hemorrhage, it has to be done while the bleeding is active. This surgical indication naturally arises only with very profuse hemorrhages. Unfortunately just in these cases in which we should expect most success from an operation, the conditions as a rule are such, that the operation forms a greater danger than the hemorrhage itself. In the first part of this paper I pointed out the fact, that with the rapidly developed exhaustion of these patients a prolonged operation must become a hazardous experiment. If we want to be reasonably certain of accomplishing anything at all, we must undertake radical, that is, prolonged operations. The quickly performed gastro-enterostomy does not answer; it is, as we have seen before, entirely unreliable. As Deaver states, gastro-enterostomy in acutely bleeding ulcers is worse than useless. Prolonged operations, however, are decidedly more dangerous, the percentage of mortality after radical operations being considerably higher than after gastro-enterostomy, particularly when the operation is undertaken under the unfavorable conditions resulting from excessive hemorrhage. When we further consider that even a radical operation does not always succeed in checking the bleeding, we cannot conceive that this uncertain and risky procedure lessens the danger of the situation. On the contrary, in profuse hemorrhage, the patient stands a better chance of recovery, if treated in the conservative manner described in this paper. It is not probable that radical operations undertaken at the time of the bleeding, will reduce the 3 per cent. mortality usually observed in excessive gastric hemorrhage. We should try, however, to reduce the mortality by improving the methods of medical treatment. In this connection I wish to plead

once more for the more frequent employment of gastric lavage as a direct means of checking the bleeding. It is certainly not superfluous to emphasize the advisability of gastric lavage, when we realize that nowadays physicians can be convinced more easily in favor of laparotomy than for the use of the stomach tube. At all events lavage should be tried before an operation is decided upon. While it can do no harm, lavage will frequently check the bleeding and postpone an operation, which may prove necessary for other reasons. I have no doubt that the good results derived from lavage will do away with the deeply rooted prejudice against using the tube in bleeding ulcer.

NORMAL HUMAN BLOOD SERUM AS A CURATIVE AGENT IN HEMOPHILIA NEONATORUM.[1]

A PRELIMINARY REPORT, WITH SUGGESTIONS FOR ITS USE IN OTHER CONDITIONS.

By John Edgar Welch, M.D.,

PATHOLOGIST TO THE NEW YORK LYING-IN HOSPITAL, NEW YORK.

(From the Laboratory of the New York Lying-in Hospital.)

In a study of a series of cases in which animal serum was administered to human beings it has been noted that certain symptoms appear regularly and in sequence. The first of these and the most frequent is fever, which is usually high and may vary from one to three degrees Centigrade. The fever is irregular and fluctuates in accordance with the amount of serum used, and remains until all other symptoms disappear. Shortly after the beginning of the fever certain rashes appear on the skin, the most troublesome of which is urticaria, which may begin at the site of injection and spread over the trunk and limbs. There may be considerable œdema in the neighborhood of the wheals, and often the itching is very intense and agonizing. Erythema usually follows the urticarial rash within two or three weeks. Scarlatiniform rashes also occasionally appear. Sometimes a morbiliform rash appears, and when it affects the face, accompanied by swelling and lacrymation, with congestion of the conjunctiva, is very suggestive of measles. The lymph nodes on the side of the body to which the serum has been administered first become enlarged and later others over the body. The enlargement is accompanied by tenderness. In some instances the joints become very painful and slightly reddened, and occasionally slight swelling occurs. General œdema of the body may occur and the weight

[1] Read at a meeting of the New York Academy of Medicine, March 31, 1910.

increase, though there is diminished ingestion of food. The œdema may be accompanied by albuminuria and casts and blood in the urine. Some rare manifestations reported are: Hemorrhage into the bowel, urethral hemorrhage, œdema of the glottis, and diffuse bronchitis.

We not infrequently hear of sudden death following soon after the administration of a single dose of antitoxin. Rosenau and Anderson, in 1906, collected 19 cases from the literature and made the statement that they knew of several more that had not been reported. We all know of instances of sudden death following antitoxin injections which have not been reported in medical literature, but if all of these, reported and unreported, were taken together, they probably would not detract from the splendid record of antitoxin more than the minutest fraction of a per cent. These results by no means suggest to us the abandonment of antitoxin, but rather that we should seek some method of separating more completely the antitoxin from the serum, which is the real source of danger.

Von Pirquet and Schick were the first to consider the aforementioned symptoms, which they found in 20 per cent. of the cases receiving antitoxin, and which they studied together as a distinct disease with its definite incubation period of eight to twelve days; they called it the *serum sickness.*

The frequency of the serum sickness depends on the amount of serum used (Park and Bolduan). When 10 to 30 c.c. of serum was used, 22 per cent. of the cases developed serum sickness. Since using concentrated antitoxin with injections of 5 to 15 c.c. of serum, the number of cases developing symptoms has been reduced to 6.5 per cent. Large injections (100 to 200 c.c.) of Moser's scarlet-fever serum produce serum sickness in 85 per cent. of the cases.

Von Pirquet and Schick first demonstrated that a second injection of serum produced more rapid and acute symptoms than a single injection. The first dose has a sensitizing effect; the condition produced is the opposite of prophylaxis and is identical with the hypersensibility produced by Richet in his experiments with congestin and called by him anaphylaxis.

Rosenau and Anderson, in their experimental work on anaphylaxis, have found that in some cases one-millionth of a cubic centimeter intraperitoneally will sensitize a guinea-pig, and that a subsequent dose ten days later of 0.1 c.c. of the same serum will kill the pig. These were exceptionally small doses, but they found the same result quite regularly when larger amounts of a serum were used. Their earlier experiments were made with diphtheria antitoxin, but later, by using normal horse serum, they demonstrated that "the toxic action . . . is caused by a principle in normal horse serum and is entirely independent of the antitoxic properties of the serum."

After establishing that the poisonous principle is inherent in this particular normal serum, they extended their investigations to determine whether it also resided in the normal sera of other animals. For this purpose guinea-pigs were used, and were injected intraperitoneally with the serum of dogs, hogs, cattle, sheep, cats, and rats. Second injections with the same serum have produced either severe symptoms or caused death, producing in these cases anaphylaxis just as does the horse serum. It has been shown that large doses of normal horse serum, as well as small ones, will produce anaphylaxis in the guinea-pigs. By this work the principle that the serum of one species of animal is poisonous and often fatal to a different species has been well established. A point of interest and much importance lies in the determination of the effect of repeated doses of alien serum on the nutrition of animals to which such serum is not fatal. Repeated injections of horse serum practised by Salter in young guinea-pigs caused retarded growth. Dr. Park's experience with repeated injections into young guinea-pigs of normal horse serum, after killing the complement by heating, is that they "tend to become cachectic and die."

Since Harvey's discovery of the circulation of the blood the medical profession at times has had great hopes of finding in the transfer of blood from some healthy source to individuals suffering disease a means of curing many otherwise refractory or incurable maladies. About the middle of the seventeenth century lamb's blood was transfused into the human subject, but it was soon learned that the operation was unsafe, inasmuch as death frequently followed, in consequence of which the practice was discontinued. Many years later direct transfusion was attempted from one individual into the vein of another by means of a cannula. Because of coagulation, thrombosis, etc., the method was abandoned. Attempts have also been made to use intravenously defibrinated blood, but the method is so beset with dangers it is no longer considered safe.

Crile has given us our most recent method of transfusion, and from a surgical standpoint it must be considered an ideal one. A record of the lives that have been saved by this procedure is glowing tribute enough to its merits without entering into any words of praise. However, even here we meet with recitals of sad experiences. It is well known to those familiar with its uses that sudden death sometimes follows the transfer of blood in this way. In these cases air embolism can be excluded as a factor, and we are left with theories to account for the fatalities. Of these, we have red cell embolism, hemolysis, and thrombosis. J. G. Hopkins has demonstrated intravascular phagocytosis of red blood cells. The spreads, made from the blood and bone marrow of a patient who had been transfused and died from the effects, showed polynuclear leukocytes, which had engulfed within their protoplasm from one to five or six red blood cells. This phenomenon suggests the speculation whether,

in the transfer of whole blood from one individual to another, the cellular elements are not just so much foreign material which the recipient must destroy and dispose of, and also whether the main virtue in transfusion does not lie in the serum alone.

Under the name of hemophilia neonatorum I report herewith a series of cases, which includes a number of bleeding babies, the etiology of the hemorrhages in which, as is usually the case, is unknown. In none of the cases was the hemorrhage due to traumatism. Bleeding appears as a rule, during the first week of life, and in this series most frequently on the second, third, and fourth days. The primary

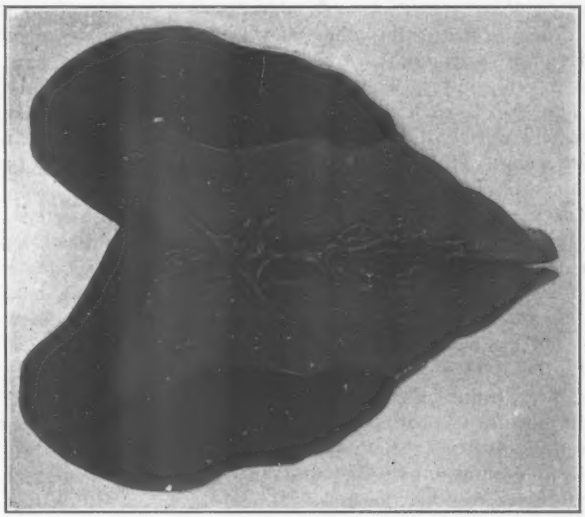


FIG. 1.—Subcapsular hemorrhage of the liver in hemophilia neonatorum.

bleeding may be from anywhere in the skin or mucous membrane surfaces. However, I have found postmortem that the principal hemorrhage may be either in the brain with extensive laceration, or in the liver (Fig. 1), in which case the capsule may be almost entirely dissected from the surface of the organ; and in addition to these, hemorrhagic spots in other internal organs and effusions of blood in the various serous cavities may be found. In some instances I have found the spinal canal filled with fluid blood. The first bleeding may be a slight oozing from the cord at its point of junction with the skin surface and not from the end of the cord due to faulty tying. This cord hemorrhage may persist in spite of all local remedies, and in the course of two or three days a considerable quantity of blood may be lost by this appa-

rently insignificant bleeding. Other bleeding may come from the gastro-intestinal tract, evidence of which is seen in the vomiting of blood or bleeding from the rectum. The lips and gums also frequently bleed. Often the severest hemorrhage appears in the skin, and as a result large hematomas may form which have no relation whatever to traumatism.

Among the list of drugs advocated as therapeutic remedies for this condition the most favorite are probably calcium salts, solutions of gelatin, and adrenalin. Numerous drugs have been employed, but the very length of the list attests their uselessness. In eighteen recorded cases of hemophilia at the Lying-in Hospital, New York, in which these remedies were used there were seventeen deaths, which demonstrates the high mortality in this disease and the futility of all previous therapeutic measures.

Having in mind the almost uniform failure of drugs in this condition and the possibility of producing serum sickness by using the serum of a different species, I decided to attempt the use of normal human serum. In January, 1909, I made my first injections of normal human serum into a bleeding baby.

Case I.—The subject was three or four days old when it began bleeding. Within twenty-four hours the body was black and blue from subcutaneous hemorrhages; there was a large hematoma occupying one-third of the scalp on one side of the head, and bleeding from the mouth and bowel. The child was so weak it could not cry out when disturbed, though it would make a feeble effort. The case was thought hopeless by the attending surgeon, who requested his house surgeon to ask permission of the parents for a postmortem examination. It was at this time I made the first injection of normal human blood serum; 10 c.c. was used and administered subcutaneously three times during the first day and once each on the following two days. Within a few hours a decided improvement was noted in the condition of the baby, in that the hemorrhages ceased, the old ones began to fade, and strength returned to the child in a very noticeable way. Within three days the hematoma of the scalp was entirely absorbed, and it was quite evident that the child was out of danger. This proved to be true, as the child left the hospital in due time with its mother without any sign of having been a bleeding baby.

Encouraged by this result, the attending physicians of the New York Lying-in Hospital have placed at my disposal for treatment with normal human serum all the bleeding babies that have appeared in their wards. Altogether I have used it in twelve cases, all of which have been cured of their bleeding sickness.

I report herewith eight additional cases, showing the variations in the temperature and weight charts.

Case II.—First child; female; full term; normal delivery. On the fifth day blood was found oozing from the vulva. During the sixth

and seventh days bleeding was continuous. Two hours after applying a fresh napkin the labia and buttocks would be smeared with blood. On the ninth day there was slight oozing from the umbilicus. There was no bleeding after the ninth day. Normal human serum was administered subcutaneously as follows: On the seventh day, three days after bleeding began, 10 c.c. in two doses; on the eighth day, 19 c.c. in two doses; on the ninth day, 22 c.c. in three doses; on the tenth day, 9 c.c. in one dose; total, 60 c.c. in four days (Fig. 2). The total loss of weight was 450 grams, which was reached on the sixth and remained through the seventh day. When the serum

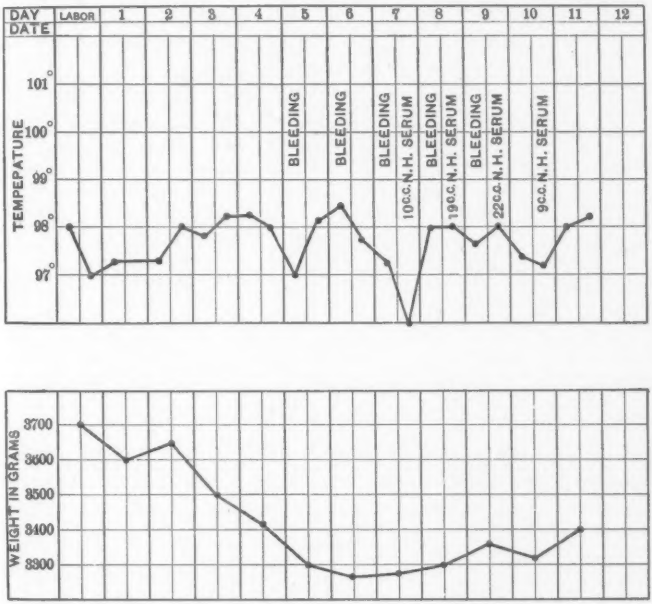


FIG. 2.—Temperature and weight charts of Case II.

was administered the weight began immediately to increase and a steady gain was made later. This baby showed a tendency to subnormal temperature, which returned to the normal after the bleeding had stopped. It left the hospital in due time in a normal condition.

CASE III.—Third child; male; full term; high forceps delivery. It showed no bleeding until the seventh day. Then a dorsal division of the prepuce was made for phimosis. During the next four days bleeding recurred about every four hours, often profuse and difficult to control. There was profuse bleeding from the stump of the cord on the seventh day, which continued on the eighth and ninth days, when the stump was invaginated. On the eighth and ninth days

there was bleeding from the lips and gums, and on the tenth day subcutaneous hemorrhages appeared on the face. Normal human blood serum was injected subcutaneously as follows: On the eighth day, one day after bleeding began, 10 c.c. in one dose; on the ninth day, 40 c.c. in four doses; on the tenth day, 12 c.c. in two doses; on the eleventh day, 14 c.c. in two doses; total, 76 c.c. in four days (Fig. 3). The weight of this child ran down steadily until the tenth day, losing altogether 750 grams (1½ pounds). Two days after receiving the serum it gained 100 grams, then lost 50, after which it held its

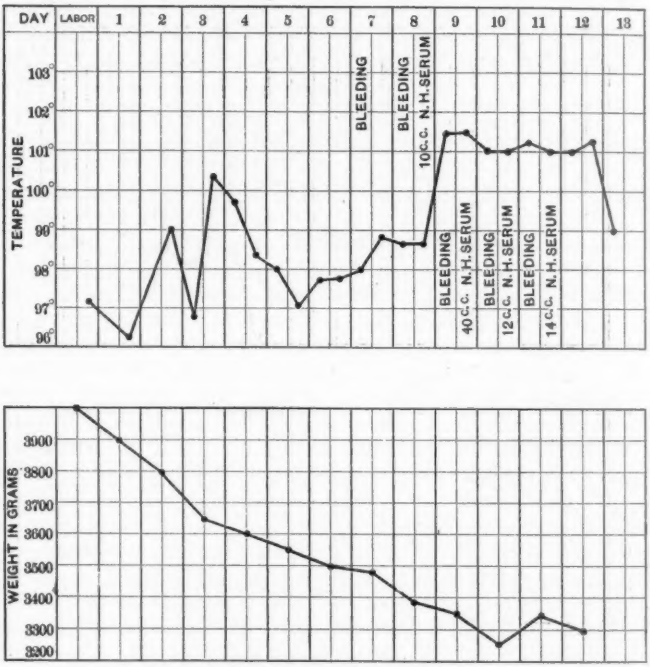


FIG. 3.—Temperature and weight charts of Case III.

own and finally gained. Directly after the bleeding began the temperature rose to 101.4°, and it did not go below 101° until the bleeding was controlled. This baby was extremely weak and was considered in a serious condition, but was finally discharged from the hospital, with the mother, in good condition.

CASE IV.—Third child; male; full term delivery by Cesarean section. On the second day there was slight bleeding from the nose and mouth, and small hemorrhagic spots appeared on the arms and back. The child had embarrassed respiration, attacks of cyanosis

and nystagmus. On the third day the hemorrhagic spots increased in size. On the fourth day profuse bleeding from the gums and from the bowels occurred. On the fifth day there was more bleeding from the mouth and rectum and more subcutaneous hemorrhages. On the sixth day profuse bleeding from the bowels. On the seventh day more subcutaneous hemorrhages in three places on the body. The baby was too weak to nurse, and was fed from a medicine dropper. At this time subcutaneous injections of normal human blood serum were begun and given as follows: On the seventh day, five days after

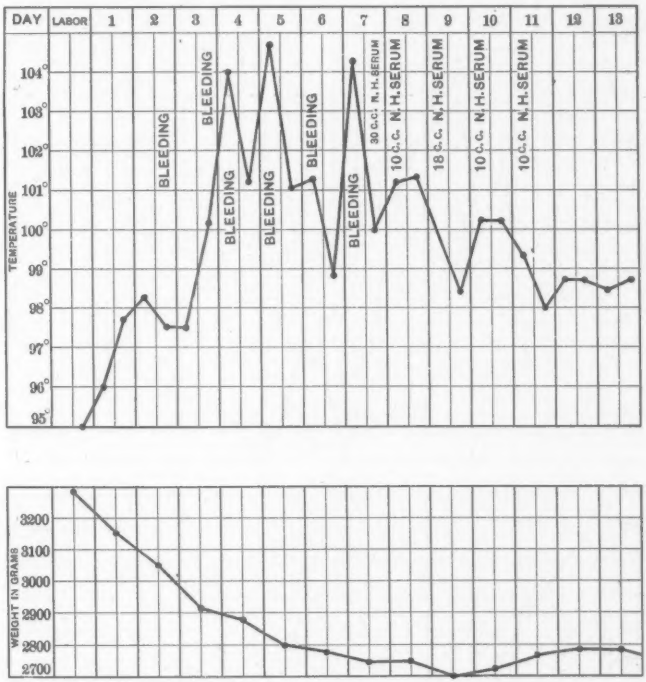


FIG. 4.—Temperature and weight charts of Case IV.

bleeding began, 30 c.c.; on the eighth day, 10 c.c.; on the ninth day, 18 c.c.; on the tenth day, 10 c.c.; on the eleventh day, 10 c.c.; that is, a total, 78 c.c. in five days (Fig. 4). Immediately after administering the serum the temperature, which on the fourth, fifth, and seventh days had been 104° to 104.6°, subsided rapidly to normal, and the weight, which had declined 550 grams, began slowly to rise. This baby had no more bleeding, but was subject to attacks of cyanosis. It had also a rotary nystagmus. On the fifty-sixth day it died, and autopsy showed the cause

to be a persistent atelectasis of the lungs involving their posterior half. None of the tissues showed any sign of hemorrhage.

CASE V.—First child; male; full term; normal labor. On the third day blood began oozing from the cord at its junction with the skin, from the foreskin, and there was copious bleeding from the nose. The stools were black, showing altered blood. A single injection of 10 c.c. of normal human serum was given, and within six hours the bleeding ceased and the stools on the following day were normal. There was no more bleeding from this baby (Fig. 5).

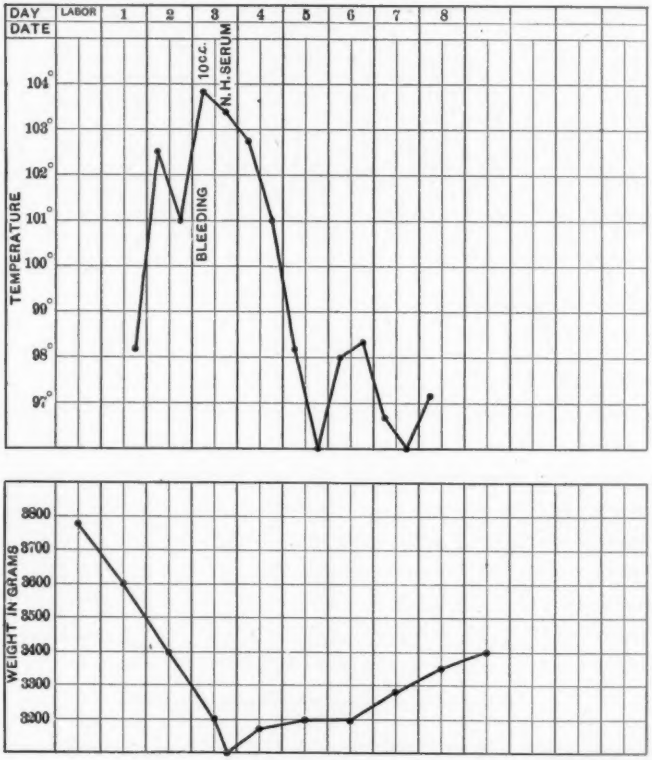


FIG. 5.—Temperature and weight charts of Case V.

CASE VI.—First child; full term; female; normal labor. On the second day it began bleeding from the nose. On the third day it bled from nose and cord, and a large hematoma appeared on the back of the head and neck which extended from ear to ear. There were also subcutaneous bleedings on the right side of the thorax, and slight

jaundice appeared. On the fourth day there was bleeding from the nose and gums and blood was passed in the stools. The hemorrhage in the neck increased, and fresh ones appeared on the scalp and right wrist. On the fifth day slight bleeding from the nose; one spot was noticed on the right knee and left elbow. Normal human serum was injected as follows: On the fourth day, two days after bleeding began, 35 c.c. in three doses; on the fifth day, 20 c.c. in two doses; on the sixth day, 29 c.c. in two doses; on the seventh day, 27 c.c.; on the eighth day, 12 c.c.; total, 123 c.c. in five days (Fig. 6). There was no more bleeding after the fifth day, and the child was discharged on the thirteenth day normal.

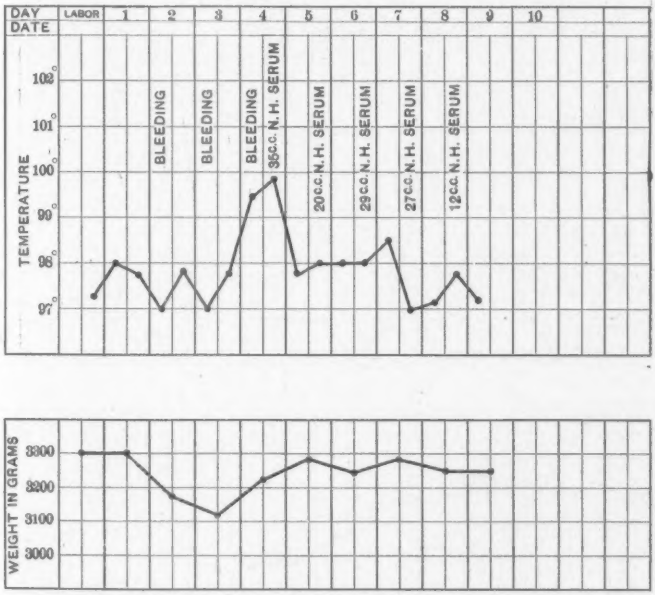


FIG. 6.—Temperature and weight charts of Case VI.

CASE VII.—First child; female; full term; normal labor. Bleeding from the cord and rectum began on the fourth day. On the fifth day bleeding from the vagina and rectum, and two subcutaneous hemorrhages appeared on the left side of the thorax. On the sixth day profuse bleeding from the cord and slight bleeding from the rectum. There was no bleeding on the seventh and eighth days, and no serum was administered in consequence. On the ninth day there was vomiting of blood and slight bleeding from the rectum. On the tenth day profuse bleeding from the cord, vomiting of blood, and bleeding from the rectum, two subcutaneous hemorrhages on

the right side of the thorax, and others on the elbows and on the back. No further bleeding after the tenth day. Normal human blood serum was administered subcutaneously as follows: On the fifth day, one day after bleeding began, 10 c.c. in one dose; on the sixth day, 20 c.c. in two doses; on the ninth day, 20 c.c. in two doses; on the tenth day, 10 c.c. in one dose; on the eleventh day, 8 c.c. in one dose; on the twelfth day, 5 c.c. in one dose; on the thirteenth day, 10 c.c. in one dose; total, 83 c.c. in seven days (Fig. 7). The bleeding in each attack was controlled on the second day. This chart illus-

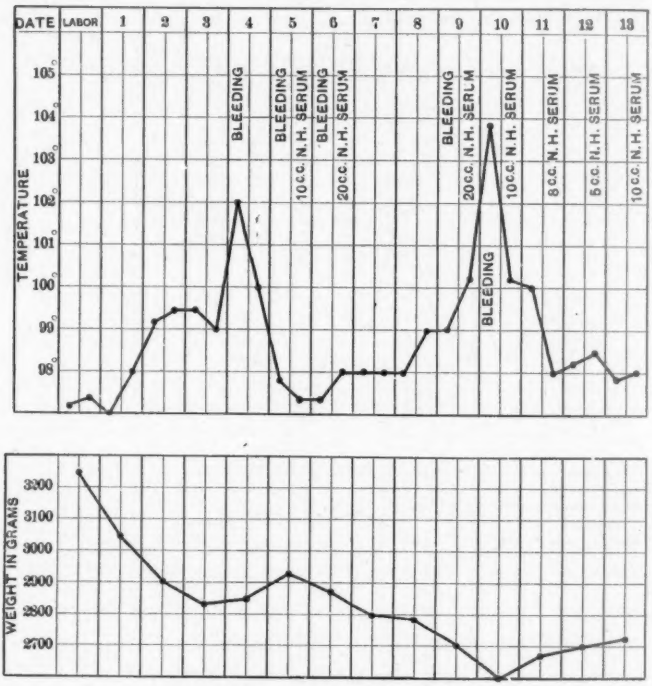


FIG. 7.—Temperature and weight charts of Case VII.

trates twice the manner in which the temperature and weight curves diverge during the bleeding, and how they approach each other when bleeding stops.

CASE VIII.—First child; male; full term; normal labor. On the third day began bleeding from the mouth and rectum. On the fourth day profuse bleeding from the mouth, nose, rectum, and under the skin covering the left scapula. On the fifth day bleeding continued. No bleeding on the sixth day. On the seventh day bleeding from the rectum. No bleeding after the seventh day. Normal human blood

serum was injected subcutaneously as follows: On the sixth day, three days after bleeding began, 7 c.c. in one dose; on the seventh day, 9 c.c. in one dose; total, 16 c.c. in two days (Fig. 8).

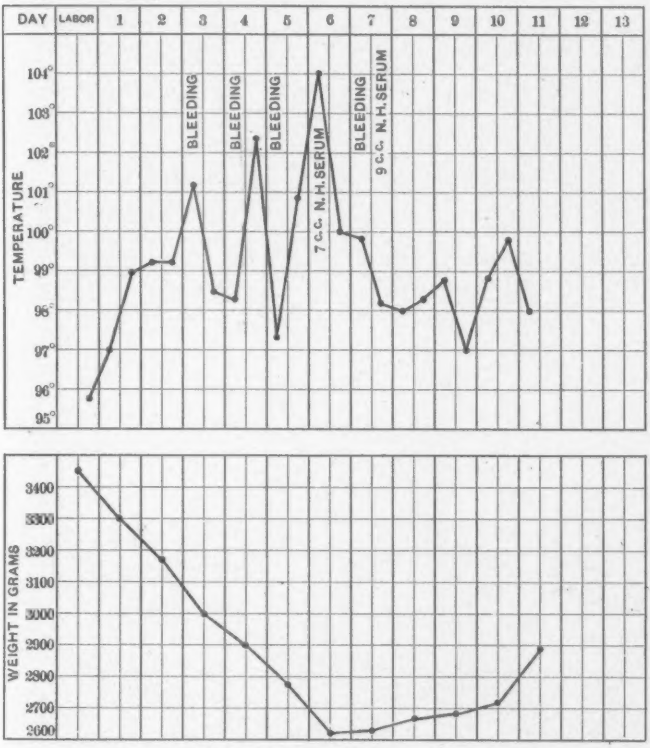


FIG. 8.—Temperature and weight charts of Case VIII.

CASE IX.—First child; full term; male. Mother had a post-partum hemorrhage. At 4 A.M. on the fourth day it had a large hemorrhage from the bowel and vomited blood-stained fluid. At 4.30 A.M. had very profuse hemorrhage from the bowel and vomited small amount of blood. At 10.30 A.M. bleeding from the rectum and vomiting of a small amount of blood. At 11 A.M. hemorrhage from the rectum, and small amount of blood vomited. Baby was very weak, not able to cry out when injected. Pale and jaundiced, waxy looking. The house physician said baby had lost half its blood. At 2.15 P.M. small hemorrhage from the rectum; 3.00 P.M., severe hemorrhage from the rectum; 7 P.M., small amount of slightly blood-stained vomitus, small blood clots in the feces; 10.30 P.M., blood clots in the

stools, slight hemorrhage from the nose, mouth, and rectum. March 23, the fifth day, 8 A.M., vomited small amount of blood; 10 A.M., large amount of blood from the rectum, which was the last bleeding. Normal human blood serum was injected subcutaneously as follows: On the fourth day, day hemorrhage began, 64 c.c. in six doses; on the fifth day, 65 c.c. in six doses; on the sixth day, 30 c.c. in three doses; on the seventh day, 22 c.c. in two doses; on the eighth day, 28 c.c. in three doses; total, 209 c.c. in five days (Fig. 9).

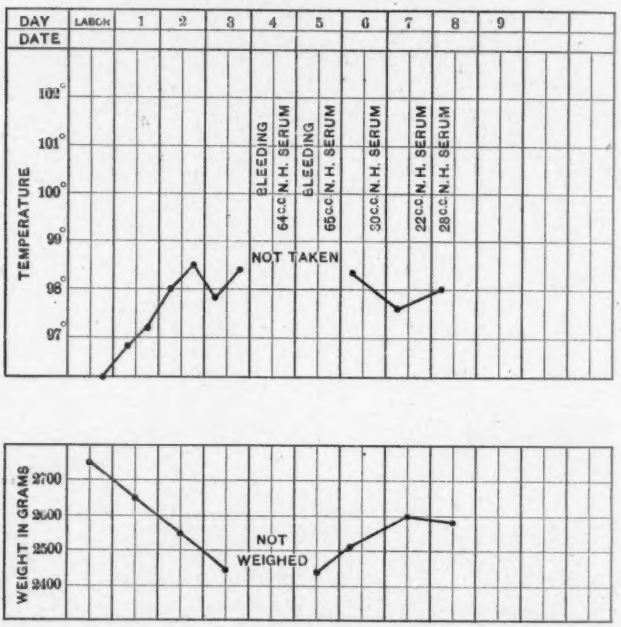


FIG. 9.—Temperature and weight charts of Case IX.

In normal human serum we find an agent that successfully controls hemorrhage in the newborn. I have not gone into the theories as to the causes of these hemorrhages. They are probably due to different factors. In none of the cases could a history of bleeding in the antecedents be obtained. It is possible that some were true cases of hemophilia, while others were due to some infection. In my postmortem experience I have found, as have others, that the hemorrhages are sometimes due to a bacteremia caused by the streptococcus, staphylococcus, and in some cases a bacillus. I have reason to believe that, even though the bleeding be due to bacteremia, the normal human serum will still be an effective therapeutic agent.

It has been demonstrated so frequently that it is now a matter of common knowledge that fresh normal human blood serum is often bactericidal. If put into the body of a baby in sufficient quantity, and kept moving by the circulation to elimination, it must surely exert this bactericidal effect. I have used it in repeated small and large doses, also in single small and large doses, and am ready to state positively that it never gives serum sickness or causes anaphylaxis in the human subject. On the other hand, it is a perfect form of food, already digested and ready to be taken up and utilized by the tissues and cells of the body, so that without dissipation of energy regeneration may progress with a maximum of efficiency. In many of these babies with bleeding from the gastro-intestinal tract, nourishment from this source is impossible. The alimentary tube is filled with decaying blood, and in most instances there is reversed peristalsis, which militates against digestion, and, added to these, there exists a clouding of the epithelium and considerable desquamation. The food cannot be properly prepared for absorption, and should it be, the circulation is so feeble as to be an obstacle to its removal into the tissues.

When placed under the skin normal human blood serum is quite readily removed from the site of injection. I have seen two ounces completely removed within five minutes by gently massaging the skin over the site of injection while administering the dose. As a further testimonal to the harmless effect of human blood serum, I will refer to some of my work in connection with eclampsia, in which I injected 150 c.c. of serum, removed from an eclamptic patient by venesection, after her twentieth convulsion, into a normal adult, within twenty-four hours, without the slightest noticeable effect, either subjectively or objectively. This patient died of her eclampsia shortly after the venesection.

It may be that the hemorrhage is partly and in some cases entirely controlled by the nutritive effect on the body tissues of the infant. In others it is possible that a thrombokinase is supplied, as suggested by Kottman and Lidsky, who obtained it from animal sera and from the filtrate of the chopped and soaked rabbit livers which they applied locally to check hemorrhages about the cord.

As to the dose of serum to be used in any given case, it should be said that this depends upon the urgency of the case. One is apt to err on the side of too small doses. It is advisable to begin with at least 10 c.c., and repeat three times per day if the infant is bleeding only moderately. In severe cases it should be given every two hours, and in larger quantities if necessary. It is very important to begin the treatment at the first indication of bleeding, however apparently insignificant. Slight bleeding of the cord may be accompanied by fatal internal hemorrhage if not stopped immediately.

The blood is very easily collected. The apparatus (Fig. 10) I have devised consists of a rubber cork through which are two perfora-

tions. Through one perforation is fitted a U-shaped glass tube, to the outer end of which is attached, by means of a piece of rubber tubing, a short aspirating needle having a No. 19 caliber. The needle is cotton-plugged into a small test-tube, in which it is sterilized. Through the other perforation is inserted a fusiform glass tube containing cotton to prevent contaminating the contents of the flask. A small suction tube is placed on this latter for drawing the blood into the flask. The needle is inserted into a vein at the elbow and

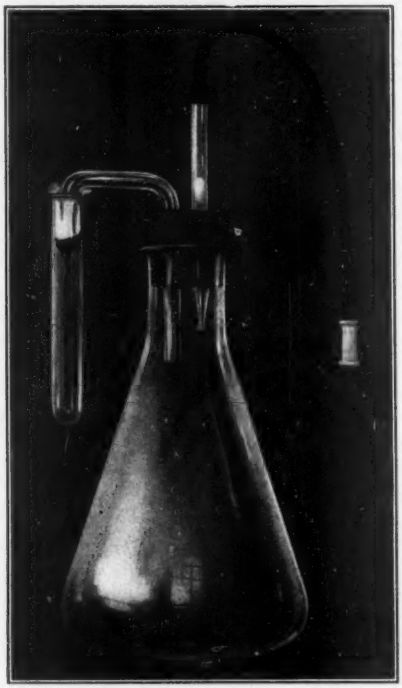


FIG. 10.—Apparatus for collecting the blood serum.

the desired amount of blood withdrawn. The blood is allowed to coagulate in a slanting position in the flask, and the serum is withdrawn as rapidly as it separates, and it is then ready for use.

I have also used subcutaneous injections of normal human blood serum in a case of streptococcemia, with an apparent good effect. The patient's temperature was normal until the third day postpartum, when it rose to 104° F. On the fourth day an intrauterine culture developed a growth of streptococci and staphylo-

cocci. A blood culture on the sixth day proved sterile. The patient's temperature remained high, so that notwithstanding a negative blood culture she was considered to be suffering with bacteremia. In consequence she was given Hiss' extract of leukocytes on the seventh, ninth, tenth, and eleventh days. The temperature seemed to react well for a few days under this treatment, but finally rose again on the twelfth day to 104.8° F., and the patient's condition was very bad. A second blood culture, made on the tenth day postpartum, developed a pure growth of streptococci.

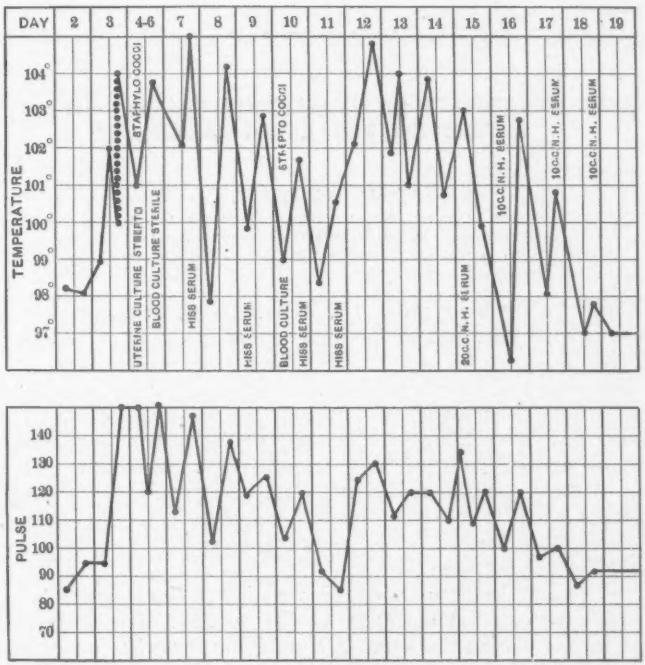


FIG. 11.—The temperature curve and the pulse rate in a case of streptococcemia.

The patient was considered in a hopeless condition from the twelfth to the fifteenth day. On the fifteenth day she received 20 c.c. of normal human blood serum hypodermicly, and on the sixteenth, seventeenth, and eighteenth days each 10 c.c. She had no rise of temperature after the nineteenth day. A blood culture made on the twenty-seventh day developed no growth of organisms. The patient was dismissed from the hospital in a normal condition. Fig. 11 illustrates the temperature curve and the pulse rate in this case.

Normal human blood serum administered hypodermicly to tuberculous individuals gives excellent results. According to Wright, normal human blood serum contains more opsonin than that of a tuberculous person, and it may be through this property, causing more complete phagocytosis, that the benefit in this condition is derived.

Normal human blood serum has a broader field of application than in the cases herewith mentioned. By means of work now in progress I hope to demonstrate its value in other conditions.

THE METABOLISM OF MYASTHENIA GRAVIS, WITH A SUGGESTION REGARDING TREATMENT.

By Ralph Pemberton, M.D.,

Woodward Fellow in Physiological Chemistry, Pepper Laboratory; Assistant Instructor in Medicine in the University of Pennsylvania; Physician to the Out-Patient Department of the Presbyterian Hospital, Philadelphia.

Through the kindness of Dr. W. G. Spiller, an opportunity has presented for the study of the metabolism in a case of myasthenia gravis.

The subject of myasthenia has received attention, in great degree, from neurologists alone, and though the clinical aspects of the disease have been known for a long time, little has been adduced to date regarding the etiology or pathology. It would seem, in view of these facts, that, except for the great rarity of the disease, attempts would have been made to approach it through other channels; but reference to the literature shows that, with few exceptions, this has not been the case.

For example, in his *Metabolism and Practical Medicine*, von Noorden devotes but one page to the question of myasthenia in general, mentioning the work of Kauffmann, who has investigated myasthenia gravis, more especially in connection with the effect of fatigue upon the nitrogenous metabolism. Kauffmann concludes that with the appearance of fatigue there is a diminution in the output of urea coinciding with an increase in the output of ammonia. He regards this as indicative of an acid intoxication, and ascribes to lactic acid the poisonous role. Lactic acid was found in large quantities in the urine on the days of work, as well as in the blood serum. In Kauffmann's case, as well as in two others reported by Mohr and Boldt, the liver was diseased, and, according to von Noorden, it seems as if the appearance of the myasthenia coincided with the extent of the intermediary products of metabolism.

Perhaps the most significant work on this subject is that of Spriggs, who has investigated the nitrogenous metabolism and the creatinin output in a variety of cases of muscular loss of function.

Spriggs finds that there is a decrease of creatinin in proportion to the decrease of muscle bulk; and that this holds true, though to a less degree, in myasthenia gravis, in which condition, however, there is, of course, little decrease of muscle volume.

When the case now under discussion was first considered with a view to chemical study, general metabolic investigations of the above nature were contemplated on the basis of there having been so little attempted in this connection; but at the suggestion of Dr. D. L. Edsall there were included examinations of the calcium and magnesium metabolism, the former of which afforded the findings of most interest.

Jacques Loeb and his associates showed a few years ago, that certain agents, when injected into the economy, cause precipitation in an insoluble form of the body calcium and produce a condition of muscular spasm. This condition could be induced by him with all the alkaline earths, except barium, and could be relieved by agents which induce the re-solution of the precipitated calcium salts or by a further injection of calcium. Meltzer and Auer have shown that rigor mortis is hastened by the injection of calcium, and under certain conditions, of magnesium salts as well; and have also called attention to the great toxicity of magnesium salts when injected into animals, even in minimal amounts. They have shown, furthermore, that there exists between calcium and magnesium an apparent antagonism, whereby animals rendered nearly moribund by magnesium can be resuscitated immediately by minimal injections of calcium.

In somewhat the same line the work of MacCallum, Voegtlin, and Halstead indicates that there exists an intimate relation between tetany and calcium metabolism. In persons the subject of extirpation of the thyroid for goitre, in whom the parathyroids have also been inadvertently removed, and in dogs in which this procedure has been experimentally performed, there occurs a loss of calcium in the urine and feces. The muscle spasm, increased respiration, and other phenomena characteristic of tetany, however, which follow upon removal of the parathyroids, can be controlled and indeed prevented by the administration of calcium salts in amounts sufficient to compensate somewhat for the loss sustained.

Such observations as the above rendered reasonable the investigation of the calcium and magnesium metabolism in myasthenia gravis in the hope of observing some relation between it and the perverted muscular functions of that condition.

The case under observation was that of an extremely intelligent man, aged about fifty-five years, presenting well-advanced features of the disease. His previous history is without special significance,

and the course of the disease need be mentioned only in so far as to state that it was in some slight degree amenable to diet and hygienic treatment. The intelligence of the patient and his coöperative efforts made possible accurate study upon him, and the subjective evidence advanced by him has been of value throughout, as an index of his progress for better or worse.

He was placed for ten days upon a metabolic diet whose content in the various features investigated either was known or could be easily determined. The features investigated were the total nitrogen, ammonia, creatinin, calcium, and magnesium, all of which were determined in the urine; while the feces were examined for total nitrogen, calcium, and magnesium. Articles of his diet in which the calcium and magnesium content were not known, were submitted to similar investigations.

The methods adopted were the Kjeldahl in the determination of nitrogen and Folin's colorimetric method in the determination of creatinin. The calcium was determined as oxide, after precipitation by ammonium oxalate and subsequent ignition; the magnesium, as oxide, after precipitation with ammonia from the calcium filtrate and subsequent ignition. During the experiment the patient was maintained, as far as possible, under the same circumstances as those under which he had been living just prior to it.

Under the conditions of the dietary administered the patient did well. The determination of the nitrogen balance over a period of six days of the seven days studied showed a nitrogen retention of about 16 grams (16.6117). In this period of six days, however, the calcium metabolism not only failed to keep pace with the nitrogen retention, but did not even maintain an equilibrium, showing, indeed, an actual loss amounting to more than 8 grams (8.4888).

Investigation of the magnesium metabolism showed no apparent departure from the normal. The ammonia output was apparently also well within the limits of health, and no indication of an acid intoxication could be induced therefrom.

Folin's observations have suggested that the creatinin output in any individual is a constant, independent of muscular exercise. Shaffer believes that in pathological subjects the creatinin is usually low, although the creatinin coefficient ($\frac{K}{N}$ per kilo body weight) shows a direct parallelism with the muscular efficiency of the individual; and indicates, furthermore, some special process of normal metabolism taking place largely, if not wholly, in the muscles. The investigations of Spriggs on the creatinin output in several of the primary myopathies, in myasthenia gravis, myotonia congenita, and tabes dorsalis, essentially corroborate this finding, and this worker believes creatinin to be a product of the internal structural metabolism of muscle and not of its contraction.

In a normal individual, Spriggs found the output of creatinin nitrogen expressed in percentage of total urinary nitrogen to be

3.9 per cent. In his series of pathological cases, the creatinin nitrogen as percentage of total nitrogen was as follows:

Normal woman	3.9
Progressive muscular dystrophy (boy of 15½ yrs.)	0.8
Progressive muscular dystrophy	1.7
Tetanus	4.0
Tetanus	2.2
Spastic paraplegia	3.7
Spastic paraplegia (dementia paralytica)	4.2
Myasthenia gravis	3.0
Amyotonia congenita (boy of 4½ yrs.)	0.3
Healthy boy (4½ yrs.)	1.0
Locomotor ataxia	3.9

The present case showed an average daily output of creatinin of 0.59155 gram, which is slightly below the low limit of excretion in health and also below the figures in Sprigg's case of myasthenia (0.689 gram). Expressed in terms of creatinin nitrogen as percentage of the total urinary nitrogen, however, the output was only 1.67, which is considerably lower than the same quotient in the case just mentioned.

Spriggs deduces from his work that in myasthenia gravis there is a diminution in the creatinin output which should be taken to indicate a connection between the excretion of creatin and muscular function apart from bulk. The present case gives color to this view, and shows, further, that the decrease may be even more marked than that which his case showed, and, indeed, sometimes almost as great as occurs in primary myopathies with loss of muscle substance.

This would seem to suggest that myasthenia gravis is a disease of disturbed internal muscular metabolism *per se*. This finding is peculiarly in consonance with the observed loss of calcium; which element is, as above stated, in close connection with the functions of muscular activity. The relation seems to be more than accidental, and calls for further investigation.

As far as can be ascertained this study forms the only attempt at a determination of the calcium metabolism in myasthenia gravis; and while one case affords insufficient grounds for positive conclusions, it is at least suggestive that, in view of the very intimate relation existing between some of the alkaline earths and muscular activities, there should be observed in this instance so distinct a loss of calcium salts. The patient has remained under the observation of Dr. W. G. Spiller, who has administered calcium lactate over a considerable period of time. Other remedial measures have been ordered, including the use of strychnine; but whether because of the calcium administered or by way of coincidence alone, the patient has markedly improved in the course of the year and a half since the observations above mentioned, and the establishment of the calcium therapy. Remissions of long periods have been reported by several observers in the course of myasthenia gravis, but, at least, they are

rare, and it may well be that we have in this definite indication of disturbed metabolism a clue to practical therapy in this disease.[1]

Through the kindness of Dr. Spiller, opportunity has been afforded for the examination of another case of myasthenia gravis with the same objects in view; but the patient was too refractory to allow of proper control of her diet, and conclusions based upon this study would be unwarranted, except in so far as to state that the results suggested no radical departure from the conditions above described.

CONCLUSIONS. The above study indicates that in myasthenia gravis there may be marked loss of calcium by the tissues even under circumstances of marked nitrogen retention.

The creatinin output in myasthenia gravis may be reduced to a point below normal; the output of creatinin nitrogen expressed in percentage of the total urinary nitrogen may be almost as low as that seen in conditions of true muscular wasting.

These facts taken together form a reasonable basis for belief that myasthenia gravis is a disease of deranged muscular metabolism, and that one at least of these two factors (that is, the loss of calcium) may stand in such a causal relationship as to indicate the therapeutic administration of that element.

I wish to express my great obligation to Dr. W. G. Spiller for the opportunity of studying the case, and also to Dr. D. L. Edsall for his suggestions and assistance during the course of the determinations.

Day.	Amount c.c.	Creatinin.	Creatinin N. as per cent. of total urinary N.	Total N. in urine.	NH_3.	NH_3 N. as per cent. of total urinary N.	Ca.	Mg.
	c.c.	Grams.	Per cent.	Grams.	Grams.	Per cent.	Grams.	Grams.
24	1550	0.6448	1.99	11.8876	1.0961	5.47	0.4550	0.2859
25	1390	0.6258	1.70	13.4848	0.7235	4.41	0.5045	0.2533
26	1415	0.5387	1.567	12.6266	0.5522	3.60	0.5515	0.1714
27	760	0.5476	1.840	10.9318	0.6610	4.055	0.4371	0.2639
28	1235	0.4281	1.23	12.7350	0.8500	5.41	0.4379	0.2906
29	1645	0.6654	1.55	15.7514	1.0322	5.39	0.5433	0.2605
30	1906	0.7437	2.12	12.8532	0.6566	4.207	0.5862	0.2840
Urinary totals		3.5493	Av., 1.668	78.3828	4.4755	Av.,4.5116	3.0714	1.5237

Ca. in feces	18.6051 grams
Mg. in feces	0.7257 gram
N. in feces	4.9156 grams

[1] In a later report the patient says that for the first time since his illness began he feels that his complete recovery is possible and not far distant.

Sum total of output:	
Creatinin	3.5493 grams
Total N.	83.2984 grams
Total NH_3	4.4755 grams
Total Ca.	21.6765 grams
Total Mg.	2.2514 grams
Average diet[2] consisted of:	
Breakfast:	
Eggs	90 grams
Bread	50 grams
Milk	420 c.c.
Butter (for fry)	40 grams
Dinner:	
Eggs	90 grams
Bread	50 grams
Milk	420 c.c.
Rice	30 grams
Supper:	
Eggs	90 grams
Bread	50 grams
Milk	420 c.c.
Apples	130 grams
Sugar	32 grams
Salt	5 grams
Total food consumed in six days:	
Eggs	1719 grams
Bread	1050 grams
Milk	8340 c.c.
Rice	210 grams
Apples	910 grams
Butter	280 grams
Salt	30 grams
Sugar	210 grams
Total grams of Ca. and N. in intake of food:	
Ca.	13.1877 grams
N.	99.9101 grams
Positive N. balance of[3]	16.6117 grams
Negative Ca. balance of	8.8888 grams

[2] In order to save space the diet tables are not given entire, but the balance was made up on the actual totals and not on the basis of an average day. The percentage content in Ca. and N. of eggs, bread, milk, rice, and butter is taken from "A Contribution to the Chemical Pathology of Acromegaly," by Edsall and Miller, University of Pennsylvania Medical Bulletin, vol. xvi, p. 143.

[3] The balance was made up on the last six days, as there was some discrepancy in the diet figures for the first day. As a matter of fact, however, this discrepancy could be safely disregarded and the amount ingested for that day assumed as practically identical with those following, as the figures are in perfect accord. This makes the metabolism studies cover, essentially, a period of seven days, one more than that actually considered. The magnesium output was so obviously within normal limits that a balance was not computed.

THE TREATMENT OF SPASTICITY AND ATHETOSIS BY RESECTION OF THE POSTERIOR SPINAL ROOTS.[1]

By William G. Spiller, M.D.,

PROFESSOR OF NEUROPATHOLOGY AND ASSOCIATE PROFESSOR OF NEUROLOGY IN THE UNIVERSITY OF PENNSYLVANIA; CORRESPONDING MEMBER OF THE VEREIN FÜR PSYCHIATRIE UND NEUROLOGIE IN WIEN, AUSTRIA.

Cases of spasticity are very numerous, and in some instances the spasticity is far greater than the motor palsy; indeed, if the implication of the pyramidal tract be slight, the spasticity, in the opinion of some, is greater than when the degeneration is intense. Spasticity is affected by various conditions. Sensory irritation, such as cold, faradic electricity, handling of the body, or voluntary movement increases the spasticity; and sleep may diminish it; so that spasticity may be less in the morning than in the evening. These effects are produced through the peripheral nerves.

Irritation of peripheral sensory fibers, as in joint disease, may increase the tonus and cause contracture. It is common to find the tendon reflexes exaggerated in the wasted limb in arthritic muscular atrophy.

Athetosis is essentially a form of spasticity, differing from ordinary spasticity chiefly in the varying degree of tonicity in the different muscles. An athetoid limb is one necessarily spastic, and first one group of muscles, then another, exhibits a predominance of the spasticity. This view has been shared recently by Schwab and Allison;[2] they state that athetosis and spastic conditions of organic origin are essentially similar processes; that athetoid movements may be regarded as variants of permanent tonic spasticities.

In order that we may have clearly in mind the rationale of the method of treating spasticity by resection of the posterior roots, it may be well to give at this juncture an elementary sketch of the chief factors concerned in spasticity.

Muscular tonus depends on the integrity of the peripheral sensory nerve fibers, of the posterior roots, of the cells of the anterior horns, and of the peripheral motor nerve fibers. Fibers pass through the brain and cord and exert a controlling influence over the spinal reflexes. These fibers have an inhibitory effect, and act as a damper on the spinal reflexes. In contrast with these are possibly other fibers whose function is to accelerate the tonus, "bahnende" fibers of the German writers. It may be partly from irritation of the latter that in slight lesions of the pyramidal tracts tonicity may be greater than in complete destruction of these tracts.

[1] A lecture delivered at the University of Pennsylvania during "Home Coming" week, March 29, 1910.

[2] Journal of Nervous and Mental Disease, August, 1909; Journal of the American Medical Association, February 12, 1910, p. 551.

The inhibitory effect of the cerebrum on the spinal reflexes is probably accomplished through the pyramidal tract. Afferent impulses are passing constantly from all parts of the body below the head to the spinal cord, and exert an influence on the cells of the anterior horns of the spinal cord, by means of which motor impulses are sent out to the muscles. It is, indeed, fortunate for us that many of these reflex acts do not enter our consciousness. When standing in a rapidly moving car we may be engaged in reading, and yet are constantly and unconsciously altering the tonicity of opposing groups of muscles. A wooden figure of the same proportions as the human body placed in a similar position would soon fall over. During life our muscles are constantly in a state of tonicity suitable for the various functions they are called upon to discharge, but in disease this condition of well-adjusted tonicity may be altered. A soldier standing "at attention," as Strümpell has said, exhibits the most perfect movement.

When some lesion damages the pyramidal tract the inhibition of the brain is removed and the spinal reflexes are left without control. The desideratum would be the restoration of the pyramidal tract, but that manifestly is impossible. The next best thing is to remove some of the afferent peripheral impulses, so that the cells of the anterior horns may not be kept in a state of overexcitement. It is possible that in lesions of the pyramidal tract the excessive tonicity is caused by the cerebellum, and theoretically it might be desirable to operate so as to influence the action of the cerebellar nuclei. An operation may be devised some day with this end in view, although at present it does not seem possible, and yet in 1905 the proposal of division of the posterior roots to influence spasticity met no response.

In this connection I quote from J. S. Risien Russell's Lettsomian Lectures:[3] "As sensation does not accrue as a result of all peripheral stimuli which evoke a central (reflex) action, Sherrington adopts 'receptor' as the neutral term to apply to the peripheral apparatus, which receives the stimulation. He points out that there are two main fields of distribution of the receptor organs—a *surface field*, which is situated at the surface layer of the organism, but external and internal, which he speaks of as exteroceptive and interoceptive respectively; and a *deep field*, which is situated in the tissues of the organism beneath the surface layer, which he designates proprioceptive. The stimulations which occur in the deep field are traceable to actions of the organism itself, as opposed to stimuli received from without. Hence the term 'proprioceptor,' which he has applied to these stimuli, which are brought about largely, as he says, through the agency of mass, with its mechanical consequences of weight and inertia, and also largely through mechanical strains and alterations of pressure, resulting from contractions and relaxa-

[3] British Medical Journal, February 19, 1910, p. 425.

tions of muscles. Among the functions subserved by the receptors of the proprioceptive, or deep field, is that of maintaining a state of tonic reaction in the skeletal muscles, which Sherrington regards as concerned with the maintenance of attitude. . . .

"Bouché has determined that fits induced by intravenous injection of absinthe in an animal deprived of one cerebral hemisphere were clonic and mainly flexor in type from the intact cerebral hemisphere, whereas the fit on the other side was tonic and chiefly extensor. Section of the mesencephalon during the fits abolished the clonic discharges, and only allowed the tonic to continue. Even more striking are the results of Leonard Hill, who was able to alter the character of the fit from tonic to clonic at will, according as he interrupted the arterial supply to the cerebrum by clamping the vessels or allowed the blood charged with absinthe to reach the brain. . . .

"Sherrington has shown that removal of the cerebrum results in what he speaks of as decerebrate rigidity, which fully accords with Dr. Jackson's view of cerebellar influx. Moreover, he found that this rigidity could be abolished, and was replaced by flaccidity in the homolateral limbs on hemisection of the spinal cord in the cervical region, which makes it evident that tonus is derived from the mesencephalon or cerebellum. Sir Victor Horsley, acting on Dr. Jackson's suggestion, divided the mesencephalon at the level of the intercollicular groove, and thus allowed of decerebrate rigidity appearing. Removal of successive sections of the cerebellar cortex produced no appreciable effect on the hypertonus until the sections involved the intrinsic and paracerebellar nuclei [nuclei of Deiters and von Bechterew]. A large horizontal lesion, separating the dorsal half of the cerebellar cortex without involving the nuclei, was also made three weeks before the division of the mesencephalon, again without any appreciable effect on the decerebrate rigidity which resulted in these animals, as compared with that which obtained when a similar section of the midbrain was performed in normal animals. Thiele, in his researches undertaken with a view to determine the source from which the hypertonus which constitutes Sherrington's decerebrate rigidity is derived, found that the chief source of this energy was at the level of the paracerebellar nuclei. Successive lesions of the mesencephalon, commencing in front and proceeding caudalward, failed to affect the decerebrate rigidity until the nuclei were reached. The experimental evidence is thus convincing, both as proving that the nuclear region of the cerebellar complex is the source of the energy, which constitutes the cerebellar influx, and as thus confirming the view enunciated by Dr. Jackson more than thirty years ago. . . .

"All the facts that have been established in regard to the cerebellum are in accord with a view that its cortex is concerned with the reception of afferent impressions which are derived from deeper structures like the muscles and joints, as well as those which the

organ receives from the labyrinth, and that efferent impulses are thus evoked from its muscles, which are responsible for that degree of tonus in the general musculature of the organism which is essential for the maintenance of attitude, and which makes it possible for coördinated movements to be executed."

These important statements show that tonicity of muscles depends on the cerebellum, and probably on its nuclei, and less so on the cerebrum. The connections of peripheral afferent fibers with the cerebellum is by means of the posterior roots. It is probable that in excessive tonicity destruction of the cerebellar nuclei would produce flaccidity. By cutting the posterior roots from a spastic limb we weaken or destroy this spasticity by removing the impulses to the cerebellum, on which organ it depends, and therefore the operation has a logical basis. Were we in a position to increase the cerebral inhibition over the motor tracts, we should not resort to resection of the posterior roots.

Various attempts have been made to overcome spasticity. In a paper read in 1905 with Dr. Frazier[4] before the New York Neurological Society on the treatment of cerebral palsies and athetosis, nerve anastomosis was discussed. At that time I recommended the resection of the posterior roots for the relief of spasticity and athetosis, but the idea was so novel it called forth no discussion, and, receiving no encouragement, I hesitated to advise further an operation that seemed too much like an experiment on man, and one not without danger. We therefore contented ourselves with an attempt to relieve spasticity and athetosis by anastomosis of one peripheral nerve with another, hoping that we might satisfactorily diminish afferent impulses, although we knew that we must diminish efferent impulses, but felt that sufficient efferent motor impulses would be left for fair discharge of function. The results seemed at first very promising. The most extreme spasticity and athetosis yielded to this treatment, but the young man on whom the operation was performed deserted the hospital and withdrew himself from our observation. When we saw him again, some three years later, athetosis in the operated limbs had almost disappeared, but contracture had become pronounced and interfered greatly with voluntary motion.

An attempt similar to ours has been made by Nutt[5] recently. This author believes that much may be gained by cerebral rest. His method differs from ours only in uniting the cut ends of the same nerve instead of uniting the cut ends of different nerves.

Schwab and Allison have proposed another method of treatment for the relief of spasticity. Their method is described as follows: "We have been led to devise a method which we shall refer to as muscle group isolation. This implies the isolation of the muscle

[4] Journal of Nervous and Mental Disease, May, 1905; American Journal of the Medical Sciences, March 1906; University of Pennsylvania Medical Bulletin, January, 1910, p 314.

[5] American Journal of Orthopedic Surgery, November, 1909, p. 151.

or the group of muscles which are at fault in the production of contracture, deformity, or athetosis. It is made effective by cutting off from the central nervous system the connection along which the abnormal impulses, active in causing spasticity or athetosis, are transmitted. This is done by a direct attack on the nerve itself, by isolating it, and injecting it with an alcoholic solution. There has resulted in the cases to be described an immediate paralysis of the physiologically stronger group of muscles without interfering with the free muscular use of the antagonists. At this point physiological exercises planned to further strengthen the antagonist may be used."

Schwab and Allison have recently (February 12, 1910) stated that they regard their method as holding considerable promise of relief. They have not attempted to cure spasticity by alcoholic injections into the peripheral nerves. They believe that by their method the peripheral pathway of the spastic impulses being temporarily blocked, their return in the original sum might be lessened.

More promising than any other method for the relief of spasticity has seemed to me for some five years the resection of posterior roots innervating the spastic limbs. He who studies disease probably has many indications justifying this operation. So far back as 1893 or 1894 I observed return of the patellar reflex in tabes after hemiplegia had occurred. This return of reflex irritability indicated that the degeneration of the posterior lumbar roots in this case of tabes had been sufficient to abolish the reflex, but that enough fibers were retained in the posterior roots to permit a return of this reflex when cerebral inhibition over the spinal reflexes was removed by degeneration of the pyramidal tract. The opposite conditions to those described in this case have been observed repeatedly. When degeneration of the pyramidal tracts has been followed by degeneration of the posterior columns extending well into the lumbar region, in posterolateral sclerosis, spasticity and exaggeration of tendon reflexes have given place to flaccidity and diminution of tendon reflexes.

Unquestionably the first operation for the cure of spasticity by division of the posterior roots was made by O. Foerster's directions.[6] His first paper was published in 1908. He relied on Sherrington's experiments on monkeys, by which it was shown that resection of one or two posterior roots produced no anesthesia, and that the sensation of any cutaneous area depends on three roots, and that not until three adjoining roots are cut does anesthesia occur. As yet satisfactory investigations concerning man are wanting, although it has been demonstrated that division of a single posterior root causes no sensory disturbance. Bruns believes that more than three roots

[6] Zeitschrift für Orthopädische Chirurgie, 1908, xxii, 1 to 3; Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, 1909, xx, 493.

may supply any cutaneous area. Foerster has never had more than two adjoining roots divided.

For the report that he makes in his second paper he selected two cases of congenital spastic diplegia, one case of tuberculous cervical spondylitis, one case of multiple sclerosis, and one case of hemiplegia. After the operation a certain resistance of the muscles persisted for several weeks in passive movement and extension of the limbs. This resistance he attributes to the pain from the irritation of the posterior roots produced by the cutting. He found at first after the operation that the leg was flexed at the knee and the thigh flexed on the hip, rotated inward, and adducted. This position alters as the cut roots degenerate, as does also the resistance of the muscles in passive movement. In spastic paralysis cutting of tendons or muscles seldom is successful. In some cases tenotomy may be necessary after division of the roots. Foerster recommends that the limbs should be placed in some corrective apparatus after division of the roots, to avoid faulty position.

The Achilles reflex was lost after the operation in Foerster's cases. He attributes this to the cutting of the second sacral and possibly also of the fifth lumbar root. It is not known positively in which posterior roots the Achilles reflex arc lies, but Foerster places it from his cases in the first and second sacral and possibly fifth lumbar roots.

Tietze[7] says the operation is not very dangerous. He had five cases with one death, and death in this case was by infection from decubitus. Gottstein had two operations and Küttner five operations and no deaths. It is, however, recognized as a major operation. Tietze refers to another fatal case in which collapse occurred before the roots were cut.

Successful cases treated by this means have been reported by Clarke and Taylor,[8] and Taylor has diminished the seriousness of the operation by devising unilateral laminectomy.

Dr. Frazier and I have reported one case in detail in which the results of the surgical treatment have been most satisfactory. Since the publication of that report the improvement in the patient's gait has been marked. He has been receiving systematic training in walking from Dr. Wm. Burdick.

The patient referred to at a previous part of this paper, on whom nerve anastomosis was performed, has also been treated by this method of resection of the posterior roots by Dr. Frazier, and in this case the cervical roots were cut. Improvement in this case also is distinct, but tenotomy may be needed on account of the shortening of the flexor muscles of the elbows.

Resection of posterior roots is useless when paralysis is intense.

In regard to some of the objections made to the treatment, I acknowledge that the operation is serious; had it not been so I

[7] Mitteilungen aus den Grenzgebieten der Medizin und Chirurgie, 1909, xx, 559.
[8] New York Medical Journal, January 29, 1909, p. 215.

should not have remained contented in 1905 in merely proposing this operation, but because of its seriousness we hesitated to carry out the suggestion. Cortical rest produced by peripheral operations seems to me a condition of little weight in the treatment of spasticity.

The overlap of sensory distributions is considerable, but this does not mean that all the posterior roots of a limb must be cut to lessen spasticity. In the lumbar region the roots at their origin are near together; and in the cervical region, though not so near as in the lumbar region, they are still close to one another, and therefore exposure of a very large area is not necessary. No one would desire complete sensory paralysis from cutting the posterior roots; a paralysis of this kind would be unnecessary, and would probably cause incoördination and defeat the object of the operation. Indeed, because of the overlapping of root distributions loss of sensation is not likely to occur. Considerable impairment of sensation developed in our first case, but this was probably because the man had had previously great impairment of sensation from his injury, and while sensation had returned, the fibers within the cord were far from normal, and therefore after the resection of certain posterior roots too few afferent fibers were left for the maintenance of sensation. Little or no disturbance of sensation was caused in our second case by extensive resection of posterior cervical roots.

In conclusion, I would say that a means has been devised full of promise for selected cases of spasticity and athetosis, and that these conditions which formerly perplexed and baffled us have in a considerable measure yielded to treatment. Undue enthusiasm is to be deprecated, as bringing the method into disrepute. Cases must be carefully selected, and only those are available in which spasticity is great and weakness is comparatively slight. The association of athetosis need not be a deterring factor, as the strength of a limb often is increased by the excessive muscular action of athetosis. As in every new method, caution is needed, and proper valuation can be placed upon the method only when more experience has been obtained.

THE PATHOGENESIS OF THE TOXEMIA OF PREGNANCY.[1]

By James Ewing, M.D.,
Professor of Pathology in the Cornell University Medical College, New York.

It is a curious maladjustment of Nature that places pregnancy among conditions difficult to separate from the pathological. We are accustomed to refer the high morbidity of gestation to the unhygienic influences of modern life, and love to refer to the Indian women

[1] Read at a joint meeting of the Pathological Society of Philadelphia and the Philadelphia Obstetrical Society, February 10, 1910.

who overtook the moving caravans of their tribes after a brief delay for parturition, but history says little about the women who never caught up with the caravan. Today obstetrics in India, China, and Africa deals with the same ponderous process and meets the same formidable hazards as in Europe and America. The comparative study of gestation reveals throughout the animal kingdom a certain lethal tendency reaching its acme in some orders of insects in which ovulation necessarily entails death. Indeed the human family is comparatively fortunate in many of its natural relations to the propagation of the species, while increasing medical intelligence should eventually shield maternity with effective safeguards not provided for the lower animals.

Of the many clinical or more obvious signs of the intrinsic pathology of gestation, some are exhibited by the great majority of gravida, while the notable minority who seem to escape are all liable to the larger accidents of parturition and the puerperal state. Anatomical studies long ago pointed to the kidney as the organ most liable to suffer damage and most responsible for the characteristic grave disorders of gestation. Leyden's "kidney of pregnancy" is firmly established as a very common and in some degree probably constant pathological condition. It consists essentially of a definite, often pronounced grade of fatty degeneration, which forms a background for the more severe lesions which are often encountered in disease, and which include acute degeneration, exudative nephritis, glomerulonephritis, or widespread necrosis, reaching at times almost complete destruction of the organ. In some respects these renal lesions and the associated symptoms are peculiar to pregnancy, and at least in their extent and severity they are not paralleled in any other autotoxic state.

For more than fifty years attention has been directed toward the liver as the probable seat of disease in several of the grave and fatal disorders of pregnancy. I find these indications very clearly apparent in von Frerich's famous work on *Diseases of the Liver.*[2] Here are presented the clinical symptoms and anatomical lesions of acute malignant jaundice, acute yellow atrophy, and eclampsia, with such accuracy and force that the hepatic lesions have never since lost the prominence which his observations helped to give them. It seems to have been the opinion of von Frerichs and Klebs[3] and others that all these diseases with pronounced hepatic lesions were closely related conditions, but in 1896 Jurgens[4] pointed out the specific anatomical changes of the hemorrhagic hepatitis of eclampsia, and he with Lubarsch,[5] Schmorl,[6] and many later writers, have endeavored

[2] Diseases of the Liver, Sydenham Soc. Trans., 1860, 192.
[3] Ziegler's Beiträge, 1888, iii, 1.
[4] Fettemboli u. Metastase von Leberzellen bei Eclampsie, Berl. klin. Woch., 1886, 519.
[5] Die Puerperaleclampsie, Erg. d. allg. Path. etc., 1896, I Abt.
[6] Path.-Anatom. Untersuch. über Puerperaleclampsie, Leipzig, 1893, Arch. f. Gyn., 1902, lxv, 504.

to establish a sharp distinction between eclampsia and other autotoxic states. Although it is a rule that auto-intoxications show mild as well as severe forms, there was for many years little tendency to connect the fatal hepatic cases with the milder disorders of pregnancy. The door to progress in this direction was opened by Lindemann,[7] 1892, who in a fatal case of prolonged pernicious vomiting described multiple neuritis and advanced degenerative lesions in the organs, especially in the liver, and referred the vomiting and ptyalism to degenerative changes in the central and peripheral nervous systems. In 1895 Eulenberg[8] collected thirty-eight cases of neuritis with hyperemesis, most of which recovered. The toxic nature of hyperemesis was here strongly indicated, as well as its probable association with lesions of the liver. Thus the basis was laid for inculpation of the liver in all the peculiar autotoxic states of gestation. The more thoroughly the organ has been examined the more constant have certain lesions been found to be, so that today one must recognize the liver of pregnancy as well as the characteristic kidney of this supposed physiological condition. In 1885 Roughton[9] pointed out that in normal pregnancy the liver often shows mild grades of just those lesions which appear in pronounced form in the fatal disorders.

According to Hofbauer,[10] 1908, the liver in pregnancy constantly shows in some degree the following alterations: (1) Fatty degeneration of central portions of lobules; (2) limitation of glycogen to the peripheral portions; and (3) bile stasis. These changes, he believes, explain the functional disorders, long recognized by French writers, which consist in diminished capacity to metabolize carbolize hydrates, a tendency toward glycosuria, and lessened detoxicating power.

The unstable nervous system of the pregnant woman has probably never escaped comment, has been the subject of much curious and some absurd speculation, and even in recent years German obstetrical opinion, led by Ahlfeld[11] and Kaltenbach,[12] was disposed to attribute to this factor the greater share of the disorders and even many of the fatalities of gestation. There is no doubt that the threshold of functional activity of the nervous system is lowered in pregnancy and that this factor greatly influences symptomatology. Blumreich and Zuntz[13] secured interesting experimental evidence in this field when they showed that pregnant rabbits subjected to

[7] Zur. path. Anat. d. unstillbaren Erbrechen d. Schwangeren, Cent. f. allg. Path., 1892, iii, 625.

[8] Ueber puerperale Neuritis u. Polyneuritis, Deut. med. Woch., 1895, 118, 140.

[9] Lancet, 1885, ii, 425.

[10] Beiträge z. Aetiol. u. z. Klinik d. Graviditätstoxicosen, Zschr. f. Geb. u. Gyn., 1907, lxi, 200.

[11] Hyperemesis gravidarum, Ptyalismus, Hysterie, Centrlb. f. Gyn., 1891, xv, 329.

[12] Ueber Hyperemesis grav., Zeitschr. f. Geb. u. Gyn., 1891, xxi, 200.

[13] Exper. u. klin. Beitr. z. Path. d. Eclampsie, Arch. f. Gyn., 1902, lxv, 737.

repeated light blows on the head responded with convulsive movements far more readily than controls.

Nervous irritability forms a part of the abnormal physiology of gestation, but that any form of intrinsic neurosis can account for the grave disorders of pregnancy is a doctrine always without scientific foundation, and now largely abandoned. An unstable nervous system is the medium of expression of some symptoms of disturbed functions of other organs, but of these disorders of function the nervous system originates none, although aggravating and perpetuating many. There are, thus, as very common changes in what passes as normal pregnancy, lesions in the chief excretory organ, the kidney, in the main organ of metabolism, the liver, and functional instability of the nervous system, the great organ of the expression of symptoms.

Starting from the basis of these essential disturbances of structure and function of the organs, the pronounced clinical forms of the toxemia of pregnancy show striking variations, which tend to impress the observer as wholly different diseases. Ordinary and pernicious vomiting, acute yellow atrophy, malignant jaundice, and eclampsia would seem, superficially, to have little relation to one another. The older writers, however, were inclined to regard eclampsia and yellow atrophy as in some way related, while several French observers were committed to the belief in the autotoxic nature of the chief disorders peculiar to pregnancy, without, however, defining the nature of the relation between them.

Isolated suggestions that many of the milder symptoms were connected with degeneration of the liver were made by Duncan[14] in 1879 and by Roughton in 1885. Before 1894 Davis[15] recognized certain forms of toxemia and based his diagnosis and treatment partly on the low urea ratio and the presence of glucose and acetone in the urine. Allbutt,[16] Bacon,[17] and Schwab[18] discussed the toxic and hepatic origin of pernicious vomiting in 1896. St. Blaise,[19] in 1898, constructed a strong argument for the view that all the mild disorders are the result of functional disturbance of the liver and constitute only a prelude to the eclamptic seizure. He emphasized especially the resemblance between these disorders and those of recognized cases of hepatism, and mentioned the low urea ratio of both conditions. In France, also, Bar[20] and Roger[21] had discussed the significance of the low urea, high ammonia, and the presence of peptones in the urine. In 1903 Whitney and Clapp[22] presented a careful study

[14] Hepatic Diseases in Gyn. and Obstetrics, Med. Times and Gazette, 1879, i, 57.
[15] Toxemia of Pregnancy, AMER. JOUR. MED. SCI., 1894, cvii, 147.
[16] Lancet, 1897, i, 570.
[17] AMER. JOUR. MED. SCI., 1898, cxv, 683.
[18] De l'autointoxications grav. et de ses consequences, Arch. gén. de méd., 1897, ii, 720.
[19] Les autointoxications gravidiques, Annal. de gyn. et d'obstet., 1898, I, 342, 372.
[20] Mercier et Menu, Traité d'accouch., 1897, iii, 703.
[21] Action du Foie sur les poisons, Thèse de Paris, 1887.
[22] Urinary Changes in Pregnancy, etc., Amer. Gynecology, 1903, iii, 121.

of the urinary nitrogen, pointing out the high proportion of nitrogen precipitable by phosphotungstic acid in eclampsia, and suggested the possibility that this sign might prove of diagnostic value. Prevailing obstetrical opinion, however, persistently ignored the importance of these observations. In 1903 Williams was fully abreast with current views when, in his *Text-book of Obstetrics*, he presented the toxic and hepatic theory merely as worthy of consideration and discussed toxemia and hyperemesis as different conditions. The first definite observation clearly indicating that the ordinary vomiting of pregnancy results from a toxic process which may end in acute yellow atrophy was made by Stone[23] in 1903 in a case studied in the Cornell Laboratory. The general conclusions drawn from this and a series of other cases I presented to the New York Obstetrical Society in 1904,[24] which were to the effect that persistent vomiting, acute yellow atrophy, and eclampsia, are closely related toxic conditions of metabolic and chiefly of hepatic origin, and that chemical analysis of the urinary nitrogen gives indications in support of this view, and should be employed in diagnosis. For three years thereafter Wolf and I[25] endeavored to determine the exact relation between changes in the urinary nitrogen and the diseases in question, publishing the results in 1907.[26] Williams,[27] and Edgar,[28] accepting the toxic theory of origin, employed urinary analyses in many clinical cases, with somewhat different interpretations and varying success. Williams, in 1906, gave a full review of current theories regarding toxemia, and endeavored to establish the urinary ammonia ratio as a safe guide in diagnosis and prognosis. Although his interpretation of the significance of the ammonia ratio was probably too rigid, his observations were of much value in drawing attention to the importance of detailed urinary analyses in toxemia.

Today the main points at issue concern the scope of the toxic form of hyperemesis, the significance of the urinary changes connected with it, the relation between the toxic symptoms of early pregnancy and eclampsia in the late months, while opinions regarding the pathogenesis of eclampsia still remain uncertain.

Regarding the relation of toxic and other forms of vomiting it is clear that any cause of vomiting may be operative in pregnancy. Yet the characteristic hyperemisis of gestation is a very definite clinical entity, and I think the only safe position to take is that it is always of toxic origin, and that an anatomical basis of the disease is found in the parenchymatous degeneration of the liver and kidneys

[23] Toxemia of Pregnancy, American Gynecology, 1903, iii, 518; New York Med. Jour., 1905, lxviii, 295.

[24] The Path. Anat. and Pathogen. of the Toxemia of Pregnancy, Amer. Jour. Obstet., 1905, li, 145.

[25] The Clinical Significance of the Urinary Nitrogen, Amer. Jour. Med. Sci., 1906, cxxxi, 751.

[26] The Metabolism in the Toxemia of Pregnancy, Amer. Jour. Obstet., 1907, lv, 289.

[27] Pernicious Vomiting of Pregnancy, Johns Hopkins Hospital Bull., 1906, xvii, 71.

[28] New York Medical Journal, 1906, lxxxiii, 897, 957.

which there is abundant reason for believing is present in every such case. It is especially important to urge that the severe and persistent cases of the characteristic vomiting are always of autotoxic origin, notwithstanding the fact that they may cease after many apparently trivial procedures. Here I am reminded of the observation of Strauss,[29] who saw long-standing hyperemesis stop when the patient was anointed with holy water forty-eight hours before her death.

The available data indicate that the ordinary vomiting of pregnancy is the early sign of a continuous train of metabolic disturbances which end in fatal hyperemesis, malignant jaundice, and acute yellow atrophy. The pathogenesis of the early toxemia is a complex subject, but the evidence points to functional disturbance of the liver of metabolic origin as the essential factor. Tracing the origin of this metabolic disturbance, one is led directly to such factors as the hereditary predisposition, the previous condition of the patient, the cessation of the menses, the influence of the nervous system, the increased demands on metabolic activity, the sudden loss of an adequate food supply, and functional disturbance of the thyroid and parathyroid glands. There is something in gestation that seems to call for a readjustment of metabolic processes. We cannot exactly define the nature of this influence, but I think its character is suggested by the fact that some animals eat little or no protein food during gestation. From the moment of conception there seems often to be a distinct reduction in the capacity to digest and adapt alien proteins, suggesting that the tissues of the embryo are built up chiefly from the maternal tissues and that a nervous mechanism shuts off the ordinary supply of alien food proteins.

The failure of menstruation seems to be an important factor in some cases, as has been shown by Keiffer.[30] There is a toxemia of menstruation which may exactly resemble that of pregnancy, both clinically and in the chemistry of the urine. Intestinal putrefaction figures prominently in a considerable group of cases with high and variable indicanuria. With a liver defective in metabolic, detoxicating, and biliary functions, a rich protein diet is imperfectly digested and metabolized, indol and other putrefactive products are formed in excess and in turn damage the liver still further, so that a vicious circle of influences is established leading at times to some very severe forms of auto-intoxication. Here, as shown by Dirmoser,[31] milk diet and intestinal hygiene may bring prompt relief.

The element of starvation is of undoubted importance in some patients, and in prolonged cases must be charged with the extreme emaciation which occurs. Indeed, it has been claimed that starvation accounts for all the urinary changes in some cases and robs these

[29] Amer. Jour. Obstet., 1906, liii, 164.

[30] La menstruation dans ses rapports avec la pathologie gén., Jour. l'Obstétrique, Paris, 1897, ii, 289.

[31] Der Vomitus Gravidarum, Wien, 1901.

urinary signs of any particular significance. As this has been the chief criticism raised against the present interpretation of hyperemesis, it seems desirable to consider it in some detail.

It may first be conceded that in some cases of hyperemesis the urinary changes are wholly or chiefly the result of starvation suddenly established in an organism requiring production of energy from an unusual source. It is then necessary to point out that starvation is itself a definite and sometimes rapidly fatal toxic process. Fasting dogs not infrequently pass into a condition of acute intoxication with increase of nitrogen output, gastro-enteritis, degeneration of the liver, and death (Schulz).[32] From the extensive literature on starvation one may refer to the recent study of Bianchi,[33] who finds that fasting mice and rabbits present granular degeneration of the liver and kidneys similar to that occurring in aseptic autolysis or produced by infusion of hypotonic salt solution. This condition he designates as *tonolysis*. In the later stages the fat and glycogen of the liver disappear, nuclear pyknosis and karyorrhexis and cell necrosis occur, and this condition he calls *toxolysis*. From simple tonolytic changes the animals may recover, but the toxolytic condition is self-perpetuating and the animals die in spite of food. In view of these observations, which are in line with many studies of similar import, it must be said that if starvation accounts for the toxemia of pregnancy, the condition still belongs among auto-intoxications, while the importance of the urinary signs of starvation becomes increased rather than diminished.

But neither the clinical symptoms nor the pathological anatomy nor the urinary chemistry of this toxemia are those of pure starvation as it occurs in other subjects. Starvation is not marked by persistent vomiting, pruritus, salivation, jaundice, maniacal delirium, and a fatal course in ten days or two weeks. The organs in fatal starvation do not show extensive grades of fatty degeneration with necrosis of large portions of the liver lobules or advanced hepatic atrophy. They show simple atrophy of liver cords, granular degeneration, and focal necroses. Regarding the significance of the urinary changes in toxemia, it is difficult to determine how far they should be referred to the simple withdrawal of food or to what extent they signify an injury to important organs. In some cases the total nitrogen is low, the urea low, ammonia high, rest nitrogen low, and acetone bodies are present. Such changes may seem to result from simple inanition, and to have no further significance, yet the validity of this view is by no means certain. In professional fasters a high ammonia ratio means the consumption of tissue proteins and fats in the absence of carbohydrates, but not that the organism is incapable of maintaining normal metabolism. In toxemia a similar ammonia

[32] Arch. f. d. gesam. Physiol., 1899, lxxvi, 379.

[33] Leber- und Nierenzellen wahrend d. Verhungerung, Frankfurter Ztschr. f. Path., 1909, iii, 723.

ratio means that the patient is incapable of digesting, absorbing, and probably of burning the supply of proteins, fats, and carbohydrates that is usually forced upon it. The urinary signs of the two conditions may be similar, but the clinical significance of these signs is entirely different.

In other cases the total nitrogen is high, 10 to 12 grams, without strict relation to the nitrogen intake, the urea and ammonia are low, but the rest nitrogen is increased 200 to 300 per cent. I know of no similar urinary findings in starvation in other subjects. They may occur, possibly in the cyclic vomiting of children, but if so they must belong to Bianchi's toxolytic stage of the process of starvation, in which there are serious lesions of the liver. Such conditions, however, are common in the toxemia of pregnancy, especially when jaundice points to disturbance of the liver. Many patients seem unable to appropriate the available food supply, and show their worst symptoms shortly after a full meal. These attacks are not due to starvation in any proper use of the word, but in all probability they result from failure to metabolize the products of digestion. Here the theory of defective desamidization seems to apply, as the rest nitrogen of these patients is usually high.

Some years ago Scholten,[34] by administering glucose, greatly reduced the high ammonia of the urine in hyperemesis without affecting the other symptoms. Wolf and I confirmed this observation for certain moderately severe cases, and drew the conclusion that hyperemesis is not an acid intoxication.

Underhill and Rand[35] have recently reported an experiment of this sort in a severe case receiving 75 to 300 grams of dextrose by rectum. During the first five days the ammonia rose in spite of the dextrose. It began to fall when the dextrose was reduced from 300 to 75 grams. The reduction from 2.46 to 0.67 gram (41 to 20 per cent.) from the fourth to the ninth day failed to bring the ammonia as low as it was before the dextrose was begun, and part of this fall must be referred to the reduction in total nitrogen from 6 to 3.24 grams. From the ninth day the ammonia rose steadily in spite of dextrose, reached a higher point than before (2.04 grams, 57 per cent.), and the pregnancy had to be terminated. On the day of the lowest ammonia the patient was not making as much urea as on the day of highest ammonia, while the symptoms were not relieved. The urea formation was therefore a better index of the patient's condition than was the ammonia under dextrose therapy. If this experiment shows anything more than unexplained variations in ammonia excretion, it demonstrates the impossibility of controlling the ammonia and the symptoms with dextrose. While the dextrose seemed to have a temporary influence in correcting the acidosis, its chief

[34] Beiträge z. Geb. u. Gyn. (Hegar), 1900, iii, 3.

[35] The Peculiarities of Nitrogenous Metabolism in Pernicious Vomiting of Pregnancy, Arch. Int. Med., 1910, v, 61.

influence was to transfer the source of energy from protein to carbohydrate, thus reducing the total nitrogen and obscuring the deficiency in urea-forming function. I interpret the experiment as showing chiefly that both the urea-forming and the glycogenic functions were deficient.

The experiments with glucose do not, therefore, rob the urinary analysis of its value as a diagnostic sign, since ammonia is a measure of a toxic form of starvation and at the same time of the urea-forming function. In spite of its antiketogenic power glucose does not greatly or permanently reduce the ammonia, and, although a nutrient, it does not relieve the symptoms. Three hundred grams of glucose ought not only to correct the acidosis, but it should relieve the symptoms of simple hunger, but its effects in hyperemesis show that this condition is something more than lack of food. Thyroid extract, which is not a nutrient, not only corrects the acidosis of toxemia, but it relieves the symptoms, probably because it improves nitrogenous metabolism and facilitates urea formation.

The high rest nitrogen of many cases of toxemia we found to be a very significant feature of the urinary changes. This increase, which is partly of amino-acids, may be missing in some cases in which the ammonia runs high, but in others it may be very pronounced, and being often the only notable urinary change, we are disposed to think that defective desamidization is an important factor in some phases of the disease. Leathes[36] recognizes the importance of this high undetermined nitrogen, but Underhill would discard entirely the theory of defective desamidization, and asserts that there is no evidence that it existed in our reported cases. Yet in support of this statement he refers only to a class of cases which were grouped together partly because they showed chiefly high ammonia and little or no sign of defective desamidization, but he ignores a larger group in which the rest nitrogen was high.

The clinical significance of the rest nitrogen has been doubted also on the ground that this fraction in many cases in which it is high is yet not above the limits observed by Folin[37] in certain apparently normal subjects. The total rest nitrogen recorded by Folin for normal subjects was usually distinctly below 1 gram, but in a very few cases for short periods it rose to 1 gram and once to 1.34 grams. Underhill assumes that such differences in the rest nitrogen of apparently healthy individuals are "merely indications of the variation which may occur in normal metabolism." Yet the validity of this assumption may be questioned. Wolf and I have examined the urine of many normal subjects, and have found, as a very general rule, that when the rest nitrogen in adult men on mixed diet rises above 1 gram, or 10 to 15 per cent., the subjects are liable to attacks of indigestion, constipation, headache, migraine,

[36] Acidosis in Pregnancy, Proc. Royal Society, 1908, i, No. 5, Path. Sec., p. 131.
[37] Analyses of Thirty Normal Urines, Amer. Jour. Physiol., 1905, xiii, 45

nervous irritability, urticaria, and pruritus or other skin affections. Johnston and Schwartz[38] have found a close relation between the rest nitrogen and the course of certain skin diseases. In all these cases the high rest nitrogen must be taken as a sign of defective metabolism, and not as an unimportant peculiarity of normal metabolism without clinical significance. I think, therefore, that one must not compare the rest nitrogen in toxemic women with that of "healthy" men on a starch-cream diet, but only with that of the subject herself when free from toxic symptoms. The rest nitrogen dropped from a comparatively high to a relatively low figure in so many of our cases when they became free from symptoms that we are disposed to maintain the opinion that this high rest nitrogen was in some way connected with the production of these symptoms..

Another source of doubt as to the dependence of urinary changes upon functional disturbance of the liver has been assumed to exist in the results of certain experimental lesions of this organ. Pearce and Jackson[39] destroyed considerable portions of the liver by injections of hemolytic serum, but found little coincident change in the urinary nitrogen. It seems doubtful if these experiments have any direct bearing on the significance of the urinary changes in toxemia of pregnancy. The hepatic lesions of toxemia are the result and not the first cause of the impairment of function. They must arise from secondary disturbance in the nutrition of the organ cells, and do not exist until that disturbance has reached a certain intensity. When one injects hemolytic serum into a healthy animal much of the liver may be destroyed, but the remaining portions preserve their functions and the metabolism is only slightly affected. When, however, the limit of safety has been passed by such procedures as the injection of acid into the bile ducts, or by the establishment of an Eck fistula, symptoms and urinary changes develop rapidly and with great violence, as in eclampsia.

Pearce and Jackson call attention to the fact that in two of their animals in which the liver showed diffuse degeneration as well as focal lesions the nitrogen partition was distinctly altered.

The dependence of urinary changes upon lesions of the liver was firmly established by Minkowski,[40] Nencki and Pawlow,[41] and Salaskin and Zaleski,[42] and it seems unlikely that this fundamental principle of experimental pathology will ever be discredited.

An obscure feature of the urinary chemistry in toxemia is the occurence of a nearly normal nitrogen partition in the late stages of prolonged and fatal cases. I can offer no satisfactory explanation for such results. They remind one of cases of diabetes in which sugar and acidosis disappear shortly before death. It seems possible

[38] New York Med. Jour., 1909, lxxxix, 535, 590, 636.
[39] Experimental Liver Necrosis, Jour. Exper. Med., 1907, ix, 552.
[40] Arch. f. exper. Path. u. Pharm., 1886, xxi, 41.
[41] Ibid., 1893, xxxii, 161.
[42] Ztschr. f. phys. Chemie., 1900, xxix, 517; 1902, xxxv, 246.

that the metabolism becomes reëstablished on a low and insufficient scale, while the patient dies from secondary degenerative processes established in the organs.

In view of these and many other uncertainties surrounding the interpretation of urinary analyses, I can only repeat that great caution is needed in basing clinical procedures on the results of these analyses. Their chief value is found as a basis for preventive measures. Our experience during the last three years has fully justified the expectations of their clinical value. They are a means of separating the safe from the hazardous pregnancy. They have repeatedly given warning of an unsafe condition and led to the use of dietetic and hygienic measures which have improved the metabolism. I have known their warning to have been persistently neglected with patients who eventually lost their lives, and whose physicians are now converts to the method.

While the practical value of the study of the nitrogen partition in these cases seems assured, the exact significance of some of the urinary changes must be sought in future investigations. Complete urinary analyses in a large number of normal pregnancies with various diets are much needed as a standard of comparison. Extended analyses of all the nitrogenous substances over long periods in toxemic cases, with careful estimation of the diet, would doubtless throw much light on the uncertain points now under discussion. The metabolism of fats, carbohydrates, and inorganic substances, as well as of the nitrogen, deserves attention. As has been urged by Leathes, it is especially the composition of the "rest nitrogen" that demands investigation, and recently there have been important contributions to our knowledge in this difficult field. Although amino-acids make a considerable part of this fraction, the peptones of the older observers, Salkowski's colloidal nitrogen precipitable by alcohol, and Savarè's[43] non-dialyzable nitrogen, all belong more or less in this category. Marriott and Wolf[44] have shown that Salkowski's colloidal nitrogen, while much increased in toxemia, does not correspond to the amino-acid fraction. Ginsberg[45] finds that the rest nitrogen is chiefly composed of oxyproteic and other amino-acids, and that the nitrogen referable to wholly unknown substances in human and dog urines is not large. This conclusion, as well as Savarè's studies, seem to strengthen the basis of the theory of defective desamidization, since a deficiency of this process would tend to increase the oxyproteic acids and other non-dialyzable protein cleavage products in the urine. Yet we are not committed to this theory as a complete explanation of toxemia, but only as a partial explanation. Its influence is most apparent in subjects taking some protein food,

[43] Der Gehalt der Frauenharns an adialyzablen Stoffen, Beitr. z. chem. Physiol., 1907, ix, 401.
[44] Colloidal Nitrogen in the Urine, AMER. JOUR. MED. SCI., 1907, cxxxiii, 404.
[45] Ueber d. Oxyproteinsaurefraction des Harns, Hoffmeister's Beitr., 1907, x, 410.

while in cases that are retaining no food and burning only body proteins its importance is less apparent.

Regarding the close relation of acute fatal hyperemesis and acute yellow atrophy the evidence seems to me conclusive. Clinically hyperemesis pursues an acute or fulminant, a subacute, or a chronic course. In the fulminant cases one finds the liver often small, of greatly reduced consistence, with extensive fatty degeneration, and central or zonal necrosis. There must be some additional factor to account for the widespread complete destruction of liver tissue seen in many cases of acute yellow atrophy, and this factor may possibly be found in the solvent action of extravasated bile. There are also indications that closer clinical observation and chemical study may reveal some specific form of intestinal putrefaction leading to polycholia, as the distinguishing element separating acute yellow atrophy from the cases not marked by jaundice. With the exception of jaundice and complete destruction of liver tissue hyperemesis and acute yellow atrophy arise under similar conditions in pregnancy, pursue much the same course, and intermediate cases between the typical forms, both clinical and anatomical, are occasionally observed.

While 60 per cent. of the cases of hyperemesis, it is said, recover, there are certain sequels which are attached to the condition. It would appear doubtful if the patient ever fully recovers during gestation, and premature ageing of the child-bearing woman may in large part be due to repeated auto-intoxication during pregnancy. Toxemia is also a fruitful source of fœtal death, and the fœtal organs show the same changes as the maternal. Obstetrics does not yet charge itself with responsibility for the condition of the viable fœtus at birth, but while there are remarkable exceptions, the infants of toxemic mothers are often imperfectly developed, sometimes show definite constitutional defects, and are especially liable to the disorders of infancy.

In the maternal organism the most important sequel of toxemia in the early months is nephritis in the later periods. That nephritis is a frequent result of the early toxemia, I am convinced is a fact from having observed several striking cases which appeared to have recovered from persistent vomiting in the early months but later developed active nephritis. In cases of eclampsia, in which nephritis is nearly constant, a history of previous toxemia can nearly always be established. In a third group of cases toxemia continues up to the outbreak of eclampsia. Although it is impossible to define the exact nature of this connection, there are a number of observations which show that several of the factors concerned in hepatic toxemia act as nephrotoxic agents. There is considerable evidence to show that the acidosis of early toxemia may contribute to the albuminuria of later months. In dogs whose livers had been injured by potassium

cyanide or chloroform Richards and Howland[46] found that small doses of indol caused severe damage to the kidney. In hepatic toxemia with intestinal putrefaction similar conditions exist, favoring unusual toxic effects on the kidney from indol and other intestinal poisons. Studying the metabolism of typhoid-fever convalescents, Wolf and I[47] found that early ingestion of meat may be followed by excessive indicanuria, excretion of unchanged amino-acids of the food, and albuminuria, constituting the so-called "febris carnis." There is here an obvious parallel with the excessive meat diet which many women indulge in after the first relief from the early vomiting of pregnancy. While none or all of these factors may fully explain the relation between nephritis and toxemia, they may render more acceptable the view that such a relation exists. St. Blaise has already discussed this subject at length.

The late nephritis of pregnancy, whatever its origin, becomes of great importance in its relation to eclampsia. The problem of the pathogenesis of this disease still seems far from complete solution.

The transfer of interest from the kidney to the liver as the organ chiefly responsible, the search, led by Weichardt,[48] for a specific poison in the placenta or syncytium, the inculpation of the fœtus as the source of the poison, and the numerous expedients employed to reproduce the disease are familiar phases of the history of research in this field. Among the most systematic efforts yet made to reach a solution of the problem, that of Dienst[49] deserves particular notice. He first reaches the important conclusion, which would seem to be final, that eclampsia is not caused by a poison emanating from the fœtus, for he found that the fibrin and leukocytes are lower in the fœtus and the thrombotic lesions appear later than in the mother. Against this view stands also the occurrence of eclampsia in cases of molar pregnancy, (Hitschman,[50] Kroemer,[51] Dienst). The placental theory he also abandons, since all previous efforts to find specific changes in the eclamptic placenta had failed and he himself had found entirely normal placentas in eclampsia. Dienst then commits himself to the theory that the thrombotic lesions and the chief symptoms of eclampsia are caused by the sudden destruction of excessive numbers of leukocytes, which he believes gather in the distended veins of the uterus and placenta and during labor discharge excess of fibrin ferment into the circulation. Several difficulties stand in the way of this hypothesis, among which are the absence of any definite cause of such destruction of leukocytes; the predominance of thrombi in the liver over those in the lungs; the occasional absence of thrombi;

[46] Archives of Pediatrics, 1907, xxiv, 401.

[47] The Nitrogenous Metabolism of Typhoid Fever, Archives Int. Med., 1909, iv, 330.

[48] Exper. Studien u. d. Eclampsie, Deutsche med. Woch., 1902, 224. Ueber Erweissuberempfindlichkeit, Centr. f. Bact., 1909, lii, 77.

[49] Pathogenese d. Eclampsie, Arch. f. Gyn., 1908, lxxxvi, 314.

[50] Eclampsie in fünf Schwangerschaftsmonate, ohne Fotus, bei Blasenmole, Centr. f. Gyn., 1904. 1089.

[51] Cited by Dienst.

the occurrence of leukocytosis after, but not before, the convulsions; and the absence of excessive fibrin deposits in the placenta. Moreover, fibrin ferment cannot account for the high blood pressure and the nephritis, two of the conditions generally regarded as most significant.

It is interesting to note that Dienst accepts the near relation or possible identity of pernicious vomiting and eclampsia and states that acute yellow atrophy must be due to the same factors as eclampsia, since convulsions are not always present in the latter condition. Eclampsia, he thinks, occurs only when the liver and kidneys are incompetent.

Hofbauer's view that an eclamptic toxin arises from the placenta is probably shared by the majority of observers. In the modified forms of a specific syncytiotoxin, now extended to include the element of anaphylaxis, it is maintained by Weichardt and others. The chief evidence in its favor is the clinical experience that the best treatment of eclampsia is immediate delivery of the placenta, and yet eclampsia occurs after delivery and in molar pregnancy.

I was at one time much impressed by the theory of a placental toxin, but have been unable to secure any definite evidence in its favor. In the histological study of a series of eclamptic placentas I found, as had others, no specific changes and sometimes no changes whatever. One's attention may be attracted by the presence of many placental blood clots in various stages of disintegration, and the suggestion arises that a hemolytic and blood-coagulating agent from such old clots may account for the hemolysis and thromboses of the disease. But I have found eclamptic placentas wholly free from such clots, and have been unable to find evidences of hemolysis in every case of eclampsia, and I do not think that a hemolytic and blood coagulating agent from the placenta will explain the lesions of the disease. Pearce concludes from a study of the action of hemolytic agents that the severe lesions of the liver produced by them are not those of eclampsia.

There have been many attempts to produce the lesions and symptoms of eclampsia by means of salt solution extracts of the placenta. These experiments usually result in extensive thromboses variously distributed according to the mode of introduction, but neither the lesions nor the symptoms exhibit the finer qualities of eclampsia, and the experimenters seem to have overlooked the fact that salt solution extracts of almost any normal organ contain nucleoproteids in a form in which they are active blood coagulants. Considering the possibility that autolytic products of the placenta might be concerned in the thrombotic lesions, Dryfuss,[52] in the Cornell Laboratory, compared the chemical composition of eclamptic placentas with normal and autolyzed normal placentas. He succeeded in showing

[52] Chem. Untersuch. u. d. Aetiologie d. Eclampsia, Biochemisches Zeitschr., 1908, vii, 493.

that the eclamptic placenta on delivery has suffered autolytic changes, as do the other organs of the body, but not that it possesses any specific toxic action. Mohr and Freund[53] believe they have found the active toxic agent of eclampsia in oleic acid, which they isolated in comparatively small amounts from the placenta, but Polano[54] discards this theory on the ground that oleic acid is not found in increased or sufficient quantities either in the placenta or in the blood. In view of these indecisive results in so many directions, I am inclined to think that a specific eclamptic toxin does not exist in the placenta, and that the therapeutic results of its early expulsion from the uterus must be explained in some other way.

Various attempts have been made to demonstrate in the blood serum a specific toxic substance in eclampsia. Chambrelent,[55] and Ludwig and Savor[56] found that rabbits succumbed to intravenous injections of either normal or eclamptic serum, but the latter was distinctly more toxic. Yet Volhard[57] and Schumacher[58] both failed to find any difference in the action of the two classes of serum. In 1906 Semb[59] tested the toxicity of eclamptic serum in rabbits previously immunized against normal serum. He hoped in this way to eliminate the toxic effects of the normal serum. Of twenty animals, ten (50 per cent.) died during the immunization against normal serum, and of the remaining ten, five (50 per cent.) died from the further injections of eclamptic serum. In the immunized animals the eclamptic serum, in doses of 4 to 6 c.c. per kilo, sometimes produced symptoms and lesions closely resembling some of those of eclampsia, but some animals were entirely refractory and showed neither lesions nor symptoms. The intraperitoneal injection of 40 c.c. of eclamptic serum proved harmless. Semb was not fully convinced by these results that he had demonstrated in the serum of eclampsia a definite toxic agent, for exactly the opposite conclusion seems to be equally justified. What Semb really accomplished appears to have been that he immunized the rabbit's red cells against the hemolytic action of human serum, but at the same time developed strong precipitins against human blood proteins, the action of which was instrumental in producing the lesions. It should be noted also that animals do not develop a true immunity against alien organ proteins, but may become increasingly susceptible to their action.

Proceeding from an entirely different point of view, Zweifel[60] concluded that lactic acid is the main toxic agent in eclampsia, and he succeeded in isolating definite quantities of this acid from the blood, but it is now generally conceded that lactic acid is one of the products

[53] Exper. Beitr. z. Pathogen. d. Eclampsie, Berl. klin. Woch., 1908, 1793.
[54] Oelsaurewirkung als Ursache d. Eclampsie, Zeit. f. Geb. u. Gyn., 1909, lxv, 581.
[55] Gazette méd. de Paris, 1894, 9th ser., i, 365, 371.
[56] Monatsschr. f. Geb. u. Gyn., 1895, i, 447.
[57] Ibid., 1897, v, 411.
[58] Beiträge z. Geb. u. Gyn., 1901, v, 257.
[59] Exper. Untersuch. z. Pathogenese d. Eclampsie, Arch. f. Gyn., 1906, lxxvii, 63.
[60] Zur Aufklarung der Eclampsie, Arch. f. Gyn., 1904, lxxii, 1; lxxvi, 536.

of the deranged metabolism of the disease, results chiefly from the convulsions, and is not the cause of these convulsions.

Thus, all efforts to discover a specific poison of eclampsia in the fœtus, in the placenta, or in the blood have failed, and some other conception of the disease would seem to be necessary.

It appears not improbable that some diffusible toxic agent may be closely connected with the symptoms of eclampsia, but the general facts of the disease strongly indicate that the eclamptic seizure can arise only in an organism long prepared for it by disturbance of metabolism and the associated organic changes. The great majority, or possibly all eclamptic seizures are preceded by a period, sometimes called the preëclamptic state, marked by elevated blood pressure, headaches, œdema, and intolerance of protein food. These are the symptoms of a nephritis, and the kidneys in fatal cases almost invariably show that a nephritis, usually of the glomerular type, has existed for some time. The urine at this time commonly shows reduction in quantity, low urea, and high rest nitrogen. These features persist throughout the eclamptic seizure, and indicate, as in the other forms of toxemia, defective urea-forming function of the liver and defective desamidization. If there is any single distinguishing causative element in eclampsia, I believe it is to be found in the nephritis and not in specific poisons from fœtus, placenta, or uterus.

The exact mode of origin of the eclamptic seizure still remains the obscure problem, but that it develops through an abrupt disturbance of metabolic functions is a view toward which attention is now generally directed. Zweifel has done much toward establishing this hypothesis, by showing the immense reduction in the so-called oxidative functions of the body, as indicated in the high ammonia and unoxidized sulphur of the urine. Wolf and I drew the same conclusion from the study of the nitrogen partition, but we believe that the metabolic disturbance is not merely defective oxidation, but is more complex, as is indicated by the high rest nitrogen. Savarè has found that the non-dialyzable fraction of eclamptic urine is ten to twenty times that of normal urine, but he has not reported on the chemical nature of the substances concerned. The metabolic disturbance appears to have the same general characters as in other forms of the toxemia of pregnancy, but it acts more rapidly and in an organism suffering from nephritis.

During the eclamptic seizure three definite effects are produced: (1) A remarkable rise in the blood pressure; (2) a pronounced injury to the nervous system; (3) coagulation of the excessive fibrinogen of the blood. That these effects are due to certain agents arising in the course of disturbed metabolism there can be little doubt. In some predisposed subjects the eclamptic seizure arises shortly after the ingestion of a full meal rich in meat. Here one looks naturally among the products of protein digestion for the toxic agent. Ammonia, amino-acids, and xanthin may be inculpated, for these are

incompletely metabolized by the injured liver and imperfectly eliminated by the kidneys. I have been much impressed by the rapid rise in the urinary ammonia during the eclamptic seizure and its rapid fall as the patient improved. This rise in the ammonia may be overlooked unless one examines the urine at three or six hour intervals. It seems to be unaccompanied by corresponding rise in the acetone bodies. It is possible that acute ammonia poisoning may be concerned in the symptoms of such cases. Ammonia is highly diffusible, raises blood pressure, is a violent nerve poison, and its effects pass off rapidly. So far as I know it does not facilitate blood coagulation, but it causes severe degeneration of organ cells and probably of leukocytes. Some years ago the Russian observers, Nencki and Pawlow, and Salaskin and Zaleski concluded that poisoning by ammonium carbamate is chiefly responsible for the symptoms following extirpation of the liver or the Eck fistula. There have been a few criticisms of this opinion, but no definite refutation of its experimental basis. Ammonia poisoning is perhaps incapable of explaining all the symptoms of eclampsia, but that it figures in the convulsions is an hypothesis which I believe is worthy of consideration.

Recent studies of the physiology of the thyroid and parathyroid glands suggest that primary disturbance of the functions of these organs may be concerned in the toxemia of pregnancy. After parathyroidectomy there is an increase in the ammonia content of the blood. The convulsions following parathyroidectomy MacCallum and Voegtlin[61] attribute to loss of calcium, but Berkley and Beebe[62] offer considerable evidence to show that these convulsions are due to some metabolic poison, possibly ammonia or xanthin, and that the calcium loss is a secondary effect associated with starvation.

It has been clearly shown that after extirpation of the thyroid and parathyroid, or of parathyroid alone, the toxic symptoms may be greatly intensified by a meat diet and reduced by milk diet. There is here a striking parallel with the toxemia of pregnancy. The meat diet offers abundant sources of ammonia, amino-acids, and xanthin. Carlson and Jacobson[63] find that in thyroid-parathyroidectomized animals the ammonia-destroying power of the liver is reduced 26 to 30 per cent., and they conclude that the increase of the ammonia of the blood is due in part to depression of the liver rather than to acidosis. In the case of certain animals in which there are no symptoms there is no increase in the ammonia of the blood and no depression of the ammonia conversion power of the liver. It is interesting to note that in these animals there is extreme salivation.

[61] On the Relation of the Parathyroid to Calcium Metabolism, Johns Hopkins Hosp. Bull., 1908, xix, 91.

[62] A Contribution to the Physiol. and Chem. of the Parathyroid, Jour. Med. Research, 1909, xx, 149.

[63] Proc. Soc. Exper. Med. and Biol., 1909, vol. 1.

The experimental studies in this field therefore have furnished important evidence inculpating the thyroid and parathyroid in the pathogenesis of the toxemia of pregnancy, favoring the view that the disorders are of metabolic origin, and that the high urinary ammonia in toxemia may result from deficiency of hepatic function rather than from simple starvation. They may also explain the remarkable therapeutic effects of thyroid extract, on which Foulkrod[64] and Ward[65] have reported, and which have been observed in a considerable series of cases soon to be reported by Beebe.

I have examined the thyroids and parathyroids in several fatal cases of toxemia, but have found no significant changes except in one case (No. 30) reported in 1907. Here one parathyroid was swollen to several times its normal dimensions and the cells were of very large size. I have found great variations in the histology of the thyroid in toxemia, but no constant changes. In some cases the gland appeared to be overacting, in others it was undersized and relatively inactive.

That pernicious vomiting, acute yellow atrophy, and eclampsia are somewhat different clinical manifestations of essentially the same disorder of metabolism is a view I ventured to state in 1904, and further evidence in its favor was offered in 1907. The evidence supporting this belief consisted in the incidence of all three disorders chiefly or exclusively in gestation, the occurrence of cases intermediate between pernicious vomiting and yellow atrophy and between yellow atrophy and eclampsia, and the frequent development of eclampsia in patients who had previously suffered from hyperemesis. Chemical studies seemed to give further evidence of the general identity of the disorders, pointing to the hepatic origin of hyperemesis and yellow atrophy and the combined hepatic and renal origin of eclampsia. Williams, however, has rejected the hypothesis of a close relation between eclampsia and the other forms of toxemia, although recognizing the connection between hyperemesis and acute yellow atrophy. He based his dissent on the absence of ammonia excess in the urine of eclampsia and on the striking differences in the lesions of hemorrhagic hepatitis from those of the other forms of toxemia. Yet the occurrence of high ammonia ratios in eclampsia has been amply proved by Zweifel, and the possibility of overlooking the rise in ammonia has already been mentioned.

Time forbids a full discussion of the significance of the hepatic lesions, but I may mention some of the features of the pathological anatomy of toxemia which warn against separating eclampsia on account of its peculiar hepatitis. The typical eclamptic liver is found chiefly in rapidly fatal cases. If the disease is prolonged, the convulsions not prominent, or if jaundice be present, one is apt

[64] Amer. Jour. Med. Sci., 1908, cxxxvi, 541.
[65] Surgery, Gynecology, and Obstetrics, 1909, vii, 617.

to find the hepatic lesion indistinguishable from that seen in some cases, which on account of the absence of convulsions are called acute yellow atrophy. On the other hand convulsions occur in some cases in which the hepatic lesion is typical of acute yellow atrophy. This intermingling of lesions and symptoms was long ago described by Virchow,[66] v. Frerichs, Klebs,[67] and Stumpf, and was early noted in my own experience in this field. When one inquires into the mode of origin of the capillary thromboses of the liver, one finds that an autolysis of the liver with injury of the endothelial cells is probably an essential underlying condition. This interpretation has been fully worked out by Konstantinowitsch,[68] has been stated in reports of my own cases, and is accepted by Hofbauer. I believe, therefore, that an acute degeneration of the liver arising in the course of acute disturbance of its metabolic functions is the essential part of the hepatic changes in eclampsia, and that the capillary thromboses are more secondary results of the action of a blood-coagulating agent in the liver and other organs. Dienst now accepts the view that eclampsia and acute yellow atrophy are due to the same general causes, the chief of which is the failure of the metabolic functions of the liver. Hofbauer expresses the same opinion.

Notwithstanding the obscurities that still exist, it must be admitted that the past decade has witnessed important progress in our knowledge of the peculiar auto-intoxications of pregnancy. The earlier studies in pathological anatomy have been reviewed, extended, and systematized, and the interpretation of lesions has been rendered more significant. The recognition of clinical symptoms, especially their wide diversity, has been facilitated, and the true import of early signs has been much more widely accepted. The dangers of chloroform poisoning and its influence in the severe hepatic lesions of many cases has been sufficiently impressed to be generally heeded. In systematic urinary analyses we have a means of recognizing the character and gravity of the metabolic disorder, as well as a basis for instituting hygienic and dietetic measures with a view of forestalling and preventing the dangerous stages of the disease. Urinary analyses may not tell when to empty the uterus, but they may suggest treatment that will make it unnecessary to empty it at all. Finally, the indications for treatment have been more clearly defined. Doubtless there are necessarily fatal forms and stages of all types of toxemia, but with the great majority of patients the relief of acidosis, the hygiene of the intestine and correction of indicanuria, the careful control of the diet, with reduction or exclusion of proteins, and the intelligent use of thyroid extract, should control the milder cases and greatly reduce the mortality in the severe forms of the disease.

[66] Centrlb. f. allg., Path., 1891, ii, 805.

[67] Ziegler's Beitr. 1888, iii 1.

[68] Konstantinowitsch, Beitr. z. Kennt. d. Leberveranderungen bei Eclampsie, Beitr. z. path. Anat. (Ziegler), 1907, xl, 483.

CHRONIC FAMILY JAUNDICE.

By Wilder Tileston, M.D.,
ASSISTANT PROFESSOR OF MEDICINE IN THE YALE MEDICAL SCHOOL, NEW HAVEN, CONNECTICUT,

AND

Walter A. Griffin, M.D.,
RESIDENT PHYSICIAN AT THE SHARON SANITARIUM, SHARON, MASSACHUSETTS.

In recent years considerable attention has been attracted to a remarkable disease, characterized by chronic non-obstructive jaundice with enlargement of the spleen, and usually occurring in hereditary form, or in several members of one family. In spite of a goodly number of reports from Germany, England, and especially from France, the condition has attracted little notice in this country, and no articles on the subject have appeared. That chronic family jaundice is far from rare is shown by the fact that we have been able, within a short space of time, to investigate four such families.

The first accurate account of the disease was given by Minkowski in 1900, though Murchison, fifteen years before, described a family showing hereditary jaundice, and Hayem, in 1898, reported, under the title, chronic infectious splenomegalic icterus, cases which have since been shown to belong to the condition in question. The family reported by Wilson in 1890 also belongs here, but was not thoroughly investigated.

The important features are as follows: Jaundice appears in several members of a family, frequently in two, three, or even four generations. It dates either from birth, or is first noticed during adolescence, and persists throughout life, yet in spite of the long duration, the patient experiences little inconvenience from his complaint, and may attain an advanced age. The growth of these children is not interfered with. The icterus is usually not intense, there are no signs of obstruction of the bile ducts, and symptoms of cholemia, such as itching, slow pulse, xanthomas, and multiple hemorrhages, are lacking. The stools are highly colored, and the urine contains urobilin, but no bile. Enlargement of the spleen, which may reach huge proportions, is almost a constant feature, while the liver is usually not at all, or only slightly enlarged. As a rule, there is a moderate grade of anemia. "Bilious attacks" are extremely common, especially in youth; after an indiscretion in diet, a period of constipation, or without obvious cause, the patient feels tired and depressed, the jaundice deepens, and there is repeated vomiting of bile. Headache, diarrhœa, and slight fever are occasionally noted. After a day or two the attack passes off, to recur usually several times a year. Attacks of abdominal pain, located in

the epigastrium or right hypochondrium, are met with in a large proportion of cases, and are due, as will be shown later, to a complication with gallstones. The enlarged spleen often causes a feeling of weight and pressure in the left side of the abdomen, and pain in this region, sometimes accompanied by a friction rub, is a not infrequent occurrence, owing to a complication with perisplenitis. A history of nose-bleed, particularly during adolescence, is almost always to be obtained, but hemorrhages from other organs, and especially from the stomach and intestines, are not met with, an important distinction from splenic anemia and cirrhosis. Apart from the attacks mentioned above, the subjects, as Chauffard aptly remarks, are rather jaundiced than sick. However, there is often a feeling of lassitude and a tendency to somnolence.

Types of the Disease. Besides the usual form in which the disease is hereditary, and others in which it is familial, in the sense that several brothers or sisters are affected while the parents are not, there is a "congenital" form, in which the disease appears in only one of a family, and dates from birth. This latter type does not differ in any way from the common form, except in the absence of heredity. Another type is the so-called "acquired" form, in which the disease appears first in childhood or adolescence, rarely later. Many of the cases are undoubtedly identical with the hereditary form, in which it not seldom happens that the jaundice is first noticed in youth (such as our Cases V, VII, X, and XII). There is always a possibility that slight jaundice was present earlier, but escaped detection. In other cases the acquired form shows some divergences from the hereditary, especially in the severity of the anemia, which may even simulate pernicious anemia. In the cases of Stejskal and Chauffard the red count fell below one million, but pernicious anemia could be excluded by the morphology of the red cells, and the presence of *increased* fragility of the red cells; in pernicious anemia the fragility is *decreased*. The postmortem appearances in acquired cases have been identical with those in the hereditary type, and for the present it is permissible to conclude that the acquired and the hereditary form are only different manifestations of the same disease, just as we see in other diseases which are usually hereditary (such as progressive muscular dystrophy) cases which are apparently "acquired."

The Jaundice. In well-marked instances the conjunctivæ are a lemon-yellow color, and the skin of the body is distinctly yellow, while the face is of a peculiar buff color which is quite characteristic. The greenish or blackish tint seen in long-standing total obstruction of the bile ducts is never present. In light cases the yellowness is apparent only on careful scrutiny. The jaundice varies in intensity from time to time, being more marked in some patients during the cold weather, in others in the summer. Fatigue and sometimes emotion may cause an increase in the jaundice, and at such times

the patients, as a rule, complain of lassitude and depression. Intercurrent diseases, and even taking cold, may cause an increase. Once present, the jaundice persists throughout life. An apparent exception to this rule is seen in Plehn's first case, who was very yellow as a child, but never later, and at sixty-one showed only anemia and enlarged spleen. (No examination of the serum for bile was made.) Poynton and a few others have observed recurrent attacks of jaundice with only anemia and splenic tumor in the intervals. As the blood serum was not examined for bile, it may be questioned if a slight degree of icterus in the interval did not escape detection.

THE URINE. The urine is almost always high colored. Urobilin is present in the great majority of cases, being missed chiefly in those of slight intensity. Urobilinogen is also almost always to be found. On the other hand, bile is absent from the urine almost invariably, and when found is usually in small quantities and as a transitory phenomenon. The twenty-four hour amount is normal. There is frequently a deposit of urates, and sometimes of uric acid; in one of our cases (VII) showing such a deposit, the total endogenous uric acid was increased. We have found the normal urinary pigment (urochrome) constantly increased, and this accounts in large measure for the reddish-yellow color of the urine, which is present even in cases showing no urobilin. Hematoporphyrin is always absent.

THE STOOLS. In all reported cases the feces have been well-colored, and in those that we have examined they have seemed to contain an excess of pigment, judging from the intense orange or brown color. A marked reaction for urobilin is obtained with corrosive sublimate, and an intense fluorescence with Schlesinger's test for urobilin. These facts, together with the urobilinuria, point to an increased secretion of bile into the intestine, and Möller has, in fact, shown by quantitative methods that the total urobilin excretion in the urine and feces is considerably increased (400 milligrams in twenty-four hours). Unaltered bilirubin is absent or present only in traces. The guaiac test for occult blood has been uniformly negative in our cases. The feces show no excess of fat, starch, or muscle fibers, and quantitative analysis in one of our cases (VII) showed normal proportions of neutral fat, fatty acids, and soaps, as was to be expected. Constipation is often present, but not with regularity, several of our patients passing two or three soft stools daily.

THE BLOOD.—The serum always shows the presence of bile pigment, but not of urobilin. The important feature, which gives our chief clue to the nature of the disease, is the decreased resistance of the red cells to hemolyzing agents, or as it is sometimes called, the increased fragility. This was first discovered by Chauffard, and has been present, with very few exceptions, in all the cases in which it was looked for. The usual method of testing for it is by mixing the red blood cells, preferably after separation from the

plasma, with hypotonic solutions of sodium chloride of varying strengths, and noting the point at which hemolysis takes place. With normal blood hemolysis begins in salt solutions of 0.44 per cent., and is complete at 0.36 per cent. In the case of chronic family jaundice, however, hemolysis begins at 0.6 per cent., or even 0.7, and may be complete at 0.5 per cent. This marked decrease of resistance is all the more important, because in chronic obstructive jaundice the resistance is normal or *increased*. As Chauffard has shown, this lessened resistance is evident also when tested with other hemolytic agents, such as eel serum and antihuman serum. Hemolysins, however, have never been found in the blood serum, though often looked for, and hemagglutinins have been found in only one case (Hawkins and Dudgeon). Hemoglobin has been found in the blood serum in only two cases, those of Bettmann and Chauffard. Bettmann's patient frequently had attacks of prostration with increased jaundice after exposure to cold. The author was able to induce such an attack artificially by means of immersion of the hands in ice water, and then found large amounts of hemoglobin in the serum and later in the urine. In Chauffard's case oxyhemoglobin was found in the serum during a routine examination. Such phenomena are probably quite exceptional in chronic family jaundice, but are interesting in connection with the hemolytic theory of its causation. They do not prove any close relationship to paroxysmal hemoglobinemia.

A moderate anemia is the rule, with red counts usually in the neighborhood of three or four millions. The lowest count in the hereditary type was 1,500,000 (Benjamin and Sluka), while occasionally normal figures are reported, and in two cases abnormally high counts (Mosse, 7,800,000; Guinon, Rist, and Simon, 7,200,000). In Mosse's case, however, the jaundice was acquired at the late age of fifty-four years, so that it may be doubted if it belongs with the disease under consideration. It differed from the ordinary type of polycythemia by the lack of cyanosis and the presence of acholuric jaundice. In the other case, also acquired, the polyglobulia was transient and accompanied by cyanosis.

The color index is usually normal, the hemoglobin being reduced in proportion to the red count. The red cells are usually well colored. There is well-marked anisocytosis, with microcytes predominating. When measurements have been made, the average diameter has been found decreased. Thus out of six cases in which we measured the cells, the diameter was decreased in five, averaging 6.5 microns, and normal in one. Usually there is little poikilocytosis, and some polychromatophilia, but punctate basophilia is rare. Reticulation of the red cells, as brought out by the so-called "vital" method of staining, is apparently a constant feature, and is considered by Chauffard an important diagnostic sign if present in a considerable proportion of the cells. Nucleated red cells in

small numbers are often found, usually in the form of normoblasts. In two of our cases there were isolated megaloblasts, of the intermediate variety; that is, with small deeply staining nucleus. The blood plates are present in normal numbers. The leukocyte count is usually within normal limits, sometimes subnormal and exceptionally increased. The differential count shows nothing striking except for a tendency toward high values for the polynuclear neutrophiles, and the occasional presence of rare myelocytes. The blood picture differs from that of the ordinary secondary anemia in the normal color index and the more frequent appearance of nucleated red cells.

THE LIVER. The liver is usually of normal size, or slightly enlarged, seldom reaching more than one finger's breadth below the edge of the ribs. Some have noted that during exacerbations of the jaundice the liver swells, to return to its former size after the attack is over. Signs of cirrhosis, such as hardness, irregularity, or marked alteration in size of the liver, ascites, and evidences of collateral circulation, are conspicuous by their absence. The bile, in the only case in which it was examined (our Case VII) was of a deep golden-red color, evidently very rich in pigment, and was sterile.

Attacks of abdominal pain resembling biliary colic have been observed in a large proportion of cases, and have been often supposed to be caused, in some mysterious way, by the disease itself. In two of our cases (VII and IX), however, gallstones were removed at operation, after which the attacks ceased, and in both our autopsies (Cases I and II) stones were found in the gall-bladder, so that we have no hesitation in declaring that these attacks are due to gallstones. A striking feature is the frequent onset of the colic at the time of puberty, a period at which ordinary cholelithiasis is seldom met with. The pain is sometimes located in the region of the spleen, and is then due to perisplenitis, for friction rubs have been heard over the spleen and inflammatory changes in the capsule have been found at autopsy. The pain of perisplenitis, however, is different from that of gallstone colic, being usually dull and not paroxysmal.

THE SPLEEN. The presence of splenic tumor forms one of the most striking features of the disease, and has often led to the false diagnosis of splenic anemia. It is practically always palpable, in well-marked cases extending down to the level of the navel, and occasionally reaching the proportions of a leukemic spleen, as in our Case VIII, in which it filled the entire left side of the abdomen. In a few instances no enlargement of the spleen was found, though all the other characteristics of the disease were present. In Case III of Benjamin and Sluka, the grandfather showed no splenic enlargement, while the son and granddaughter both were typical cases with very large spleens. There is therefore no reason to make a separate category out of the cases without splenic tumor.

THE HEART. This organ shows no abnormalities, except for a soft systolic murmur in the pulmonary area, due to the anemia.

THE METABOLISM. Tests for alimentary glycosuria and levulosuria have been almost constantly negative. In our Case VII, however, a moderate excretion of sugar was noted after the ingestion of glucose, and also after levulose; it was not determined in the latter instance whether the sugar excreted was dextrose or levulose. In this same case normal values were found by one of us (Tileston) for creatin, creatinin, urea, and ammonia; the patient was on a creatin-free diet.

COMPLICATIONS. True gout has been associated in a few instances, notably in the family described by Murchison, and in our Cases I, IV, and XI. Articular pains, usually without joint changes, are somewhat frequently reported, and great importance has been attached to them by French observers, who make them a part of the "hepatic diathesis" ("hépatisme" of Glénard). They are not a constant feature by any means, and in our opinion have no important bearing on the disease. The various forms of chronic arthritis and arthralgia, particularly in elderly persons, are so common that it is easy to get a history of them in some members of almost any family. Urticaria is not uncommon. The complication with gallstones has already been discussed.

PATHOLOGY. Only eight autopsies have been performed, in the cases of Minkowski, Vaquez, Gandy and Brulé, Oettinger, Strauss, Wilson, and our Cases I and II. The cases of Strauss and Oettinger were acquired, the others hereditary; the pathological picture was the same in both types. The liver has been found normal in size, with no obstruction of the bile ducts, and no cirrhotic changes. Evidences of cholangitis have been lacking, except in our Case II, in which there were dilatation and thickening of the common duct, evidently secondary to gallstone disease. In all cases there was a considerable deposit of brownish pigment within the liver cells; this pigment contained iron in Vaquez's case, in Minkowski's it did not. In five of the eight cases stones were found in the gall-bladder. The spleen is greatly enlarged (up to 1000 grams), and usually shows signs of old perisplenitis; the increase in size is due mainly to increase of the pulp, the trabeculæ being, as a rule, not much enlarged, and the follicles normal, or, as in the case of Wilson, sclerosed. Microscopically the striking feature is the marked engorgement with blood; this in one-half of the cases was most marked in the pulp, the sinuses containing little blood. There is more or less pigment in the organ, usually within endothelial cells. The amyloidosis found in our Case I was probably to be attributed not to the disease itself, but to the complication with gout. The kidneys in Minkowski's case contained a very large amount of iron, both as pigment and in combination with an albuminous body; in the other cases there was little pigment in the kidneys. The bone marrow

is found in a state of intense reaction; there is red marrow in the femur and numerous normoblasts, myelocytes, and polynuclear cells are seen.

HEREDITY. The disease is in most instances an exquisitely hereditary affection, frequently involving three or even four generations. It is transmitted equally by the male and by the female, and Wilson's statement that it is usually transmitted from father to daughter, and from mother to son, does not hold good for most instances. There are families in the literature in which only females are affected, and others in which the males are the ones to show jaundice. In a large series, however, the sexes are involved about equally (55 males and 45 females in 100 cases). There seems to be no racial predisposition. Some of the children almost always escape, and the offspring of those who do are always free from the disease.

ETIOLOGY AND PATHOGENESIS. Various theories have been propounded to account for this strange disease. Two may be dismissed from the start—the second theory of Pick, of a congenital communication between the bile passages and the lymphatics, and Hayem's latest view, that it is due to syphilis. The former is disproved by the autopsies, the latter by the entire lack of proof of the existence of syphilis in these families, and by negative Wassermann reactions in the four cases of Weber and Dorner.

The icterus present is certainly of the type known as polycholic, or, perhaps more correctly, pleiochromatic. That is to say, it is due to an excess of biliary pigment, not to obstruction of the bile ducts. This is shown by the fact that the stools are well colored, and the total urobilin output increased, as shown by Möller, and by the absence of any obstruction of the bile ducts, small or large. The presence of *temporary* obstruction of the bile ducts must be admitted for a few cases, in which with increased jaundice and usually colicky pains in the abdomen the stools became clay-colored, but these exceptions are readily explained by a complication with gallstones, which is common.

Let us next consider the first theory of Hayem, that the icterus and splenic enlargement are due to a chronic cholangitis. This view has very little in its favor, for it is difficult to conceive of a chronic infection of the bile-passages sufficient to produce jaundice dating from birth, and persisting through many years, and yet leaving no traces visible at the postmortem examination.

Minkowski believes that the disease is due to a congenital perverted function of the liver cells, by virtue of which the bile is secreted in part into the lymphatics instead of into the bile capillaries. Under normal circumstances the liver cells secrete sugar into the lymphatics and bloodvessels, and bile into the bile passages. It is easy to conceive that this selective action might be interfered with, so that part of the bile would go the wrong way. This hypothesis would account for the jaundice, but not for

the excess of bile pigment, nor for the enlargement of the spleen. Moreover, the jaundice may be explained solely on the ground of pleiochromia, for it has been shown that an excess of bile pigment is accompanied by increased viscidity of the bile, which raises the pressure in the bile passages and thus produces in a sense a mechanical obstruction to the flow of bile, and consequently jaundice.

The discovery by Chauffard of the increased fragility of the red cells threw a new light on the disease, and apparently explained the various phenomena in a satisfactory way. The red cells, being unduly susceptible to the action of hemolyzing agents, are readily destroyed, and this leads to the anemia which is so constant a feature. The bone-marrow is stimulated by the deficiency in red cells to increased activity, shown in the circulating blood by the presence of nucleated red cells and at times an increased proportion of polynuclear leukocytes, and a few myelocytes. The increased destruction of red cells leads to an increase in the material (free hemoglobin) out of which bile pigment is made, and hence to pleiochromia and icterus. Such a "hemolytic icterus" can be produced experimentally, as Lesné and Ravaut and others have shown, by the injection of hemolytic agents, which is followed by jaundice, increase in size of the spleen, and, depending upon the size of the dose, by the appearance of urobilin, bile, or hemoglobin in the urine.

Since no hemolysins can be demonstrated in the blood, the increased destruction of red cells probably takes place not in the blood, but in the spleen, that "graveyard of the red corpuscles." This leads to increased work on the part of the spleen, and hence to the progressive enlargement of the organ.

This hemolytic theory offers the best explanation of the phenomena observed, and is the one generally accepted by recent writers. The ultimate cause of the increased fragility of the red cells remains to be discovered. Two hypotheses are possible: (1) That there is a congenital defect of metabolism leading to the production of toxic substances deleterious to the red cells; and (2) that there is a congenital defect in the blood-forming organs.

Terminology. As often happens in diseases of obscure causation, a multitude of names has been proposed, depending on the theory of the writer with regard to etiology, and whether the hereditary, the familial, or the congenital aspect is emphasized. For example: Chronic infectious splenomegalic icterus, chronic acholuric hereditary jaundice, congenital hemolytic icterus, chronic family cholemia, etc. Until more is known about the pathogenesis, the term chronic family jaundice may be recommended on the ground of simplicity and clearness.

Other Familial Diseases Associated with Jaundice or with Splenic Tumor. There are a few other affections which may occur in several members of a family, and show more or less resemblance to chronic family jaundice.

1. *Congenital Obliteration of the Bile Ducts.* This process, due either to congenital malformation or to inflammatory changes, leads to intense obstructive jaundice, visible at birth. It is incompatible with the long continuance of life. In some cases, however, there is only stenosis of the common duct, and the patient may live many years, with jaundice and partial decolorization of the stools; the gall-bladder is greatly dilated, from which fact and the time of appearance of the icterus the diagnosis can be made.

2. *Fatal Icterus Neonatorum without Obstruction of the Bile Ducts.* Very rarely families are met with in which almost all of the children, and they are many, become deeply jaundiced a few days after birth, and usually die within a period of days or weeks, often with convulsions. Bile is found in the urine, but the stools are well colored. Those infants which do not die early recover from the jaundice completely, but are very anemic for a while afterward. At autopsy nothing has been found to account for the jaundice; in particular there has been no obstruction of the bile passages, and no evidence of septic processes or syphilis. A curious feature is the "Kernicterus" of Schmorl; the ganglia at the base of the brain are an intense yellow, while the rest of the brain is only slightly icteric; the yellow areas show necrosis of the nerve cells. This type of icterus is peculiar to jaundice of the newborn, and has been reported chiefly in connection with the family type.

3. *Juvenile Family Cirrhosis.* Cirrhosis occurring in two or more children of a family has been described by a number of writers. A few of these cases may be attributed to hereditary syphilis, some others to the use of alcohol or other irritating substances; thus, the two children reported by Jollye (*Brit. Med. Jour.*, 1892, i, 858) both drank vinegar in large quantities. For the majority, no cause could be made out. The course resembles that of Hanot's cirrhosis, ending fatally before the twentieth year. The growth is usually stunted.

4. *Familial Splenomegaly of the Gaucher Type.* This truly remarkable disease, first described by Gaucher in 1882, is characterized by enormous enlargement of the spleen (up to 7000 grams) lasting over many years, usually occurring in several members of a family, and affecting females almost exclusively. The liver is always considerably enlarged. Anemia is seen, and brown pigmentation of the skin, but jaundice is seldom, and ascites never, present. The histological appearances are pathognomonic. The spleen, bone-marrow, lymph nodes, and in the liver the ramifications of Glisson's capsule show large numbers of peculiar cells, with small nuclei and much protoplasm. Marchand has recently shown that the large size of the cells is due to a deposit of a homogeneous material like hyaline, the nature of which could not be determined.

Diagnosis. Chronic family jaundice is easily recognized, if the disease is only borne in mind. The great enlargement of the

spleen with anemia has led to the false diagnosis of splenic anemia, or Banti's disease; the latter diagnosis was made in our Case XII by a well known European clinician. The occurrence of jaundice in other members of the family, the chronicity, the early onset, the presence of bile in the feces and its absence from the urine, the changes in the blood, and the enlargement of the spleen without enlargement of the liver or indications of cirrhosis, are the important diagnostic points. From juvenile cirrhosis it is distinguished by the absence of marked enlargement of the liver, the absence of stunting of the growth, the absence of bile in the urine, and the course of the disease. Splenomegaly of the Gaucher type may be excluded by the presence of jaundice, the absence of marked enlargement of the liver, and by the fact that Gaucher's disease is familial but not hereditary. The acquired form of chronic family jaundice is distinguished from pernicious anemia by the increased fragility of the red cells in the former, and by the morphology of the blood. The frequent complication with gallstones has led to the diagnosis of jaundice due to obstruction of the common duct by calculi. This error can be avoided by attention to the above mentioned points.

PROGNOSIS. The prognosis is good so far as life is concerned, absolutely bad with regard to recovery. The prospects are good that some of the offspring will be free from jaundice.

TREATMENT. No measures have any effect on the jaundice or splenic tumor, not even the Röntgen rays. The anemia is said to have been benefited in certain cases by the use of iron, while arsenic is useless. The most that can be done is to regulate the life of the patient in such a way as to avoid the factors that tend to increase the symptoms (fatigue, excitement, indiscretions of diet, etc.). It should be realized that attacks of abdominal pain are not due to the disease *per se*, but to a complication with gallstones, and the patient should be given the benefit of modern surgical treatment, which has been neglected heretofore in all cases except VII and IX of our series.

In concluding we present the reports of thirteen cases, occurring in four families. The first of these families was investigated by Dr. Griffin, the others by Dr. Tileston. To economize space, many details have been omitted. In the urine sugar was always absent, and also acetone and diacetic acid. Urochrome was increased in all but Case XI. Albumin was absent unless otherwise specified.

Family I. Jaundice in at least seven members in three generations. Autopsies in two cases.

This family is remarkable for the frequency with which the condition has been associated with gallstone colic (five out of seven cases), and with gout.

CASE I.—O. S., male. Concerning his parents little is known, but a cousin of his father was jaundiced for many years, and suffered from severe attacks of colic. O. S. was the third of thirteen children,

ten of whom lived to grow up. One brother (H. S. S., Case II) had the same disease, and a sister was jaundiced all her life, and suffered from gallstones. O. S. was jaundiced from birth, suffered frequently from attacks of biliary colic, and died at the age of seventy-four. Of his four children, the first two were jaundiced (Cases III and IV).

Autopsy, May 22, 1900, Harvard Medical School, U—00—15, performed by Dr. F. T. Fulton, to whom we are indebted for the notes. There are extensive gouty lesions, consisting of marked deformity of the fingers and toes, with many sodium urate deposits (tophi) in the vicinity of these joints, and in the kidneys. The *spleen* is much enlarged, and firm; the capsule is thickened, with fibrous tags adherent. On section the trabeculæ are prominent, the follicles not easily made out, the pulp not increased. The *liver* is not enlarged, of normal consistency, and on section brownish red. The *gall-bladder* is considerably distended with dark green bile, and contains 13 pigmented calculi. The bile passages are normal. There are old adhesions between the gall-bladder and the foramen of Winslow. The *kidneys* are small, granular, the capsule adherent, the cortex thinned, the pelvis dilated. The left kidney contains some cysts and a small abscess. There are also hypertrophy of the prostate, arteriosclerosis, hypertrophy and dilatation of the heart, and acute pericarditis.

Microscopic Examination of the Spleen. In frozen sections treated with iodine the walls of many of the smaller vessels, and certain areas closely surrounding these vessels, are stained a mahogany-brown. Sections stained in the usual way show considerable congestion, and a general increase of the interstitial connective tissue. The pulp consists of lymphocytes and red blood cells. Throughout the pulp there is considerable golden-yellow pigment, chiefly within endothelial cells. The lymphoid cells of the follicles have almost entirely disappeared, their place being taken by small pinkish masses of hyaline material (amyloid); the walls of the smaller arteries are distinctly thickened and hyaline. "The pigment is probably derived from red blood corpuscles" (F. B. Mallory).

Microscopic Examination of the Liver. Frozen sections show no excess of fat. With iodine the walls of the smaller interlobular vessels, and small scattered areas among the liver cells give the reaction for amyloid. There is no increase of the interstitial connective tissue, and the bile capillaries are normal. There is considerable brownish pigment within the liver cells. In minute areas the liver cells are entirely gone, their place being occupied by masses of amyloid.

Microscopic Examination of the Kidneys. There is a marked chronic diffuse nephritis with extensive amyloid infiltration; also an acute inflammatory process in the collecting tubules. (Ascending infection). No pigment is seen.

CASE II.—H. S. S., brother of O. S. (Case I). When first seen in July, 1903, for bronchitis, he was seventy years old. He said he had been slightly jaundiced all his life. Examination showed icterus of the skin and eyes, great enlargement of the spleen, which reached from the sixth space to the level of the navel, and a liver of normal size; myocardial insufficiency. January 4, 1904, he was seen again for a severe attack of pain in the right hypochondrium, with tenderness over the region of the gall-bladder, fever, and leukocytosis. The stools were dark colored and the urine free from bile, while the skin was more yellow than usual. The spleen had not changed in size. This attack of cholecystitis lasted, with intermissions, for six weeks. On February 8, 1907, he was seized with his final illness, a lobar pneumonia, to which he succumbed on the 19th. An autopsy was performed by Dr. L. J. Rhea, of the Department of Pathology, of the Harvard Medical School, who has very kindly placed the notes at our disposal.

Autopsy U—07—18. February 19, 1907, by Dr. L. J. Rhea. The scleræ and skin have a distinctly yellowish tint. *The spleen* is markedly increased in size, and is united by firm adhesions to the diaphragm. The consistency is somewhat increased. On section it is deep red in color; the follicles are easily made out, the trabeculæ are just visible. *The liver* is apparently not larger than normal, the cut surface dark brownish red. The bile ducts stand out rather prominently. The common duct is patent. There are dense adhesions between the gall-bladder and the duodenum. The walls of the gall-bladder are thickened, and its cavity filled by a large black calculus. No stones are in the common duct or in the bile ducts within the liver. The common duct is quite markedly dilated and its walls thickened. There are also resolving pneumonia, chronic myocarditis, generalized arteriosclerosis, mural thrombi in the heart, chronic adhesive pleurisy, chronic nephritis and a persistent thymus gland.

Microscopic Examination. Spleen: The capsule is considerably thickened by dense fibrous tissue. The organ contains a large amount of blood which is in the pulp, not in the sinuses. The latter are narrow and appear compressed. Scattered throughout the organ are a few endothelial cells containing brownish pigment; some of the endothelial cells lining the sinuses, and in the capsule, contain similar pigment. *Liver:* There is a *slight* increase in the connective tissue between the columns of liver cells. The latter show quite a large amount of pigment in the form of fine scattered granules. The bile ducts are everywhere patent and their walls are not thickened. The sinusoids are moderately distended with blood and show some increase in lymphocytes, and a good many endothelial cells, which are phagocytic to red blood corpuscles, and polynuclear leukocytes. *Kidney:* There is a sclerotic process involving small localized areas.

Scattered tubules show numerous small brownish pigment granules within the epithelial cells.

CASE III.—H. B. S., aged fifty-five years, son of O. S. (Case I). First child. He has been jaundiced since birth, but the color now is less intense than formerly, having faded in the last twenty years. "Slow fever" (probably typhoid) in youth. Until he was forty he was subject to frequent attacks of gallstone colic so severe that operation was asked for, but refused by the surgeon on account of the long-continued jaundice. He has bled profusely from the left nostril at times, but does not bleed much after cuts. Feces and urine have been always dark. He has been troubled for a long time by rheumatic pains, with some deformity of the smaller joints.

Physical Examination, February, 1910. The skin has a yellowish tinge, evident on close inspection; the conjunctivæ are more deeply yellow. The liver is slightly enlarged to percussion and the edge is palpable on deep inspiration about two fingers' breadths below the costal margin. The spleen is enlarged to percussion and palpable at the edge of the ribs with deep breathing. *Urine:* High-colored, with deposit of urates. Bile pigment and urobilin both absent. *Blood:* Leukocytes, 13,200; moderate poikilocytosis, slight polychromatophilia. Differential count: Polynuclear neutrophiles, 80 per cent.; small lymphocytes, 13 per cent.; large lymphocytes, 7 per cent.; eosinophiles, 0 per cent. No nucleated red cells. The *serum* contains bile pigment (iodine test.)

R. S., the son of this patient, aged twenty-six years, has never been deeply jaundiced, though the color of his skin has always been dark. He has been subject "all his life" to attacks of vomiting, with pain in the epigastrium, sometimes in the right hypochondrium. Appendectomy done three years ago has had no influence on the attacks. Stools always colored so far as known. Examination shows nothing abnormal except a slight icteroid tint of skin and conjunctivæ. No enlargement of the liver or spleen could be made out. This case is probably one of chronic family jaundice, but in the absence of splenic enlargement and definite jaundice the diagnosis is not certain.

CASE IV.—O. A. S., aged fifty-one years. Brother of H. B. S. (Case III) and son of O. S. (Case I). Second child. He probably has been slightly jaundiced all his life, though he did not notice it until adolescence. The yellow color has never been marked, but is slightly greater during digestive upsets. Stools always brown. He has a tendency to indigestion, but there are no attacks of vomiting or abdominal pain. "Slow fever" as a boy, pneumonia at twenty-nine. During the past twenty-five years several typical attacks of pain in the great toe (gout).

Physical Examination, February 1910. Well developed and nourished. Skin sallow, conjunctivæ slightly yellow. *Spleen:*

Enlarged, from the sixth space to three fingers' breadths below costal margin. *Liver:* Not enlarged. No tophi.

CASE V.—M. S., aged twenty-three years. Daughter of O. A. S. (Case IV). Though always subject to "bilious" attacks with vomiting, she was never jaundiced till eight years ago, when, after typhoid fever, she began to have attacks of pain in the region of the liver, with subsequent passages of gallstones. The stools have been searched for gallstones, and about 200 have been recovered, none larger than a grape-seed. Stools always brown, urine sometimes high colored.

Physical Examination, February, 1910. Rather slightly built, but appears healthy. Skin and conjunctivæ slightly yellow. The *spleen* reaches from the seventh rib to the costal margin, where it is palpable. *Urine:* Bile pigment and urobilin absent. *Blood:* Red cells, 2,084,000; leukocytes, 5800. No nucleated red cells. Slight anisocytosis and poikilocytosis. Differential count normal.

CASE VI.—M. S., aged twenty-two years. Son of H. H. S. (Case II). Fifth child. He was born jaundiced, and has remained so ever since. Usually moderate, the yellow color at times becomes very conspicuous, and then he does not feel so well. Since the age of fourteen he has had "bilious" attacks about twice a year, with nausea, vomiting, diarrhœa, anorexia, and fever (up to 101.4°). Duration one or two days. *Never colic. Nosebleed* frequently. The stools have always been dark, the urine high-colored. The bowels move usually twice a day. The patient has been under observation since 1903, during which time there has been little variation in the condition, except that the jaundice has decreased somewhat; the size of the spleen has remained unaltered.

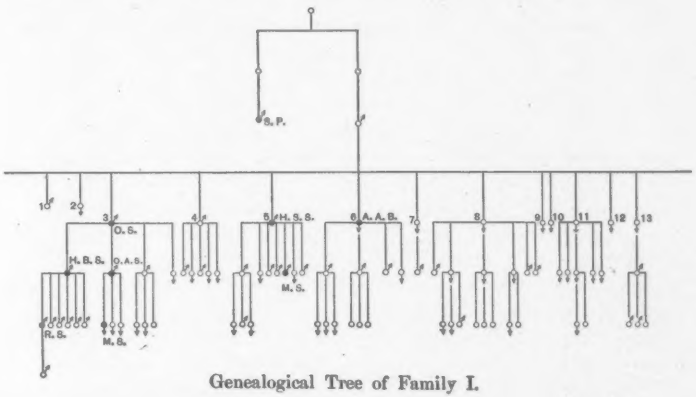
Physical Examination, January 23, 1910. Tall, active, slender youth (six feet two and one-half inches), weighing one hundred and sixty-eight pounds in clothes. Slight jaundice of the skin and conjunctivæ. *Spleen:* From the seventh space to level of navel, 17 cm., hard, rounded. *Liver* not enlarged to percussion, edge just palpable on deep inspiration. Heart not enlarged, systolic murmur in pulmonary area. *Urine:* Bile absent, urobilin sometimes present in traces, sometimes absent, urobilinogen in traces, urochrome abundant. Indican increased. *Feces:* Dark brown, urobilin present. Microscopically normal. *Blood:* Red cells, 4,144,000; leukocytes, 5000 and 9000; differential count normal. No nucleated red cells.

The accompanying family tree chart will serve to render more clear the relationships of the various members of the foregoing family.

Family II. Chronic jaundice in brother, sister, and first cousin once removed.

CASE VII.—We owe the chance to study this patient to the kindness of Dr. C. Allen Porter. W. B. W., Mass. General Hospital, No. 162,879. Aged thirty-nine years, married, no children. *Family history:* Mother died of "cirrhosis of the liver, never jaundiced"

(probably chronic family jaundice). A first cousin of mother, now forty-one years old, has been icteric since childhood. A sister of the patient, ten years older than he, was jaundiced as far back as he can remember, and had attacks of colic; she died at twenty-one years, of pneumonia. A brother, now fifty years old, has at times yellowness of the eyes, never of the skin. *Past history:* At the age of fourteen the patient noticed a yellow color of his skin, which has persisted ever since, with variations. Attacks of pain in the epigastrium with vomiting began when he was fifteen, and became more frequent and severe as he got older. In 1892 cholecystotomy and removal of 483 gallstones. The spleen was found enlarged at this time. Two later operations to close biliary fistula. Fourth opera-



Genealogical Tree of Family I.

♂ ♀ — *Male and female unaffected by the characteristic.*
♂ ♀ — *Male and female affected by the characteristic.*
♂ —— *An individual with a disease which may possibly be associated with the characteristic.*
○ —— *An individual of unknown sex.*

tion in 1905, with removal of many small pigmented calculi. Since then, no further attacks of colic. The patient had bleeding hemorrhoids in boyhood, and *nosebleed* rather frequently, especially five years ago. There has been an ill-defined pain in the right shoulder ever since the last operation. Present illness, March, 1909: Has had a continual ache in the region of the spleen for several months, and feels tired and miserable. Appetite good, bowels inclined to be costive. Has had itching at times, but only of the hands and feet. A fifth operation was performed March 23, 1909, by Dr. C. A. Porter, for the cure of a hernia in the scar of the old wound, and for exploration of the biliary system. The gall-bladder was incised and contained no calculi; no obstruction of the bile ducts could be found.

Physical Examination. Well developed and nourished, considerable pallor. Face a peculiar buff color; the rest of the skin distinctly yellow, conjunctivæ more so. Heart slightly enlarged to left, soft systolic murmur in pulmonary area. Systolic blood pressure, 130. *Liver:* Not enlarged nor palpable. *Spleen:* Much enlarged, hard, smooth, not tender; the long axis very obliquely placed, measures 22 cm. The spleen extends from the seventh rib to the level of the umbilicus, and nearly to the middle line. *Blood:* The serum was reddish yellow and gave a strong reaction for bile. The resistance of the red corpuscles was very kindly tested for us by Dr. F. P. Gay, and a decidedly increased fragility was found. The figures for the hemolysis were as follows: 0.4 per cent. salt solution, 100 per cent.; 0.45 per cent. solution, 60 per cent.; 0.5 per cent. solution, 20 per cent.; 0.6 per cent. solution, 15 per cent.; 0.7 per cent. solution, 10 per cent. Normal blood gives little or no hemolysis with 0.5 per cent. salt solution.[1] There was moderate anemia, with red counts ranging from 4,400,000 to 4,116,000; hemaglobin, 80 per cent. (Sahli); color index, I. White counts, 7200 and 8100. Differential count normal. Polychromatophilia and anisocytosis present. Most of the smears showed a few normoblasts, and once an "intermediate" megaloblast was found.

Urine. The urine was frequently examined, and was always of a high reddish yellow color. Urobilin was constantly present and bile pigment absent. The twenty-four-hour amount normal. Indican increased once, normal at other times. A uric acid deposit was often observed.

Feces. Usually one or two stools a day of a rich orange color, formed, soft, time of passage nineteen hours. Strong reaction for urobilin. During a period when Blaud's pills were being taken, the stools were a deep olive-green color. This disappeared as soon as iron was discontinued, and was probably due to oxidation of bilirubin to biliverdin by the iron. A single stool, when patient was on a purin-free diet, showed a water content of 87 per cent. and normal proportions of neutral fat, fatty acids, and soaps. (Total fat, 29 per cent. of dried stool; of this, there was 38 per cent. neutral fat, 26 per cent. fatty acids, 36 per cent. soaps.)

Stomach Examination. No fasting contents. After Ewald breakfast hypoacidity (free HCl, 0.01 per cent.; total acidity, 0.03 per cent.)

Bile. Some of the bile was obtained aseptically at the operation, and examined. Cultures, both aërobic and anaërobic, made by by Dr. Oscar Richardson, proved sterile. The bile was transparent, and of a deep golden-red color, evidently due to an abundance of bile pigment. Reaction neutral. No macroscopic mucus. Mucin present by acetic acid test. Bilirubin and bile acids present, albumin absent. Sediment negative.

[1] For the method, see Gay, Jour. Med. Research, 1907, xvii, 321.

Metabolism. In view of the present interest in creatinin, it was thought desirable to determine the amount of this substance. The patient was put on a creatin-free and purin-free diet, and after a preliminary period of three days, the urine was collected. The methods employed were, for the total nitrogen, the Kjeldahl me hod; for ammonia, urea, creatin, creatinin, the Folin methods; for uric acid, the Folin-Schaffer method. The determinations were made in duplicate. We are greatly obliged to Professor O. Folin for the use of his laboratory and for advice. The figures obtained are shown in the following table:

Date.	Total N. Grams.	NH_3 as N. Grams.	Urea as N. Grams.	Uric acid. Grams.	Creatin. Grams.	Creatinin. Grams.	Creatinin. Milligrams per kilo body weight.
April 16-17	10.81	0.60	8.63	.....	0.066	1.364	21
April 17-18	10.07	0.51	8.12	.....	0.046	1.304	20
April 18-19	9.65	0.61	7.71	.....	0.061	1.208	19
July 8-9	13.13	....	....	0.785	0.000	1.374	20

The values obtained for creatinin and urea are normal, those for ammonia are somewhat high, and the endogenous uric acid is distinctly increased. In the first period the uric acid could not be quantitated because part of the uric acid was precipitated spontaneously.

Family III. Four members affected in three generations.

For the opportunity to study this family we are greatly indebted to Dr. W. H. Smith, of Boston.

CASE VIII.—J. N., aged fifty-five years, of Irish descent, only child. *Family history:* His mother was the color of saffron as long as he can remember, twenty years or more. Her three sisters were all free from jaundice. The patient has had five children; the first was a girl and escaped the disease; the second (Case IX) and third (Case X) are both yellow; the fourth, male, died at the age of seventeen months, unaffected; the fifth, also male, was born jaundiced, and died when five days old. *Personal History:* He has been jaundiced since boyhood. The color is sometimes an intense lemon-yellow, but usually only moderate. It increases after fatigue and "catching cold," but exposure to cold does not affect it. The urine has always been high-colored and the stools brown. Nose bleed during adolescence, never "bilious attacks," or itching. He often has a tired feeling, and a tendency to sleep a great deal, but his general health is better now than when he was younger. Four years ago he had an attack of tremendous pain in the epigastrium lasting several hours (gallstone colic). There were several similar attacks that year, none since.

Physical Examination, March 1910. Small man, height, five feet four inches; weight, one hundred and eight pounds; skin and conjunctivæ of a light yellow color; acne of face. Heart not enlarged, soft systolic murmur in pulmonary area, systolic cardiorespiratory murmur at base, venous hum in neck. Pulse, 76. *Spleen:* Greatly enlarged, reaching from the eighth rib to the level of the anterior superior spine of the ilium, and to the middle line, so that it fills the left half of the abdomen. The surface is hard, smooth, not tender. *Liver:* Not enlarged nor palpable. *Blood:* Red-cells, 3,608,000. Hemoglobin, 70 per cent. (Sahli). Color index, 1. Leukocytes, 6000. Differential count: Polynuclear neutrophiles, 77.25 per cent.; lymphocytes, 19.75 per cent.; mononuclears and transitionals, 2.25 per cent.; eosinophiles, 0.5 per cent.; mast cells, 0.25 per cent. One "intermediate" megaloblast. Anisocytosis present; average diameter (100 cells), 6.48 microns, smallest cell, 4.3, largest, 8.6 microns. No poikilocytosis nor punctate basophilia, slight polychromatophilia. *Urine:* Orange colored, slightest possible trace of albumin, bile absent, urobilin and urobilinogen present. Sediment, no casts or blood. *Feces*: Formed, color a rich golden ochre, acid. Microscopically, numerous starch granules, no excess of fat or muscle fibers; the solid particles are intensely bile-stained. Marked reaction for urobilin, traces of bilirubin.

Case IX.—E. N., aged twenty-three years, son of J. N. At the age of eight he became jaundiced, without other symptoms. As a boy he often felt listless and suffered from nose-bleed. From the age of twelve to fourteen he had pain in the right shoulder, and at fourteen began to have attacks of typical *biliary colic*. Two years later he had 12 gallstones removed at operation; since then there has been no more colic. The jaundice deepens after unusual fatigue, and is more marked in the summer than in the winter. Minor illnesses of any sort cause an increased yellowness. There have been no "*bilious attacks.*" Enlargement of the spleen was first noted in 1907, by Dr. W. H. Smith. The patient does not feel sick at all, and seems alert and active.

Physical Examination, Februray 1910. Rather slightly built, well nourished, skin and conjunctivæ a lemon-yellow color. Heart negative except for a slight systolic murmur in the pulmonary area. Pulse normal in rate. *Spleen:* Considerably enlarged, reaching from the eighth rib to 1 cm. above the navel, long axis 17 cm. *Liver:* Not increased in size. *Blood:* Red cells, 4,032,000. Hemoglobin, 70 per cent. (Dare). Color index, 0.9. Leukocytes, 13,000 at 4 P.M. The fresh blood stained with brilliant cresyl blue shows reticulation in about 10 per cent. of the red corpuscles. In stained smears there is distinct anisocytosis, with decreased average diameter (6.62 microns). No polychromatophilia nor punctate basophilia. No nucleated red cells, blood plates normal. Differential count: polynuclear neutrophiles, 71.25 per cent.; lymphocytes, 21.5 per cent.;

mononuclears and transitionals, 5.75 per cent.; eosinophiles, 1.25 per cent., mast cells, 0.25 per cent. *Urine:* Orange, bile pigment absent, urobilin and urobilinogen in large amounts. Indican not increased. Uric acid and oxalate crystals in the sediment. *Feces:* Formed, color raw Sienna, microscopically normal. Urobilin strongly positive.

CASE X.—F. N., aged twenty years, daughter of J. N. For five years past slight yellowness of the eyes and skin has been noticed. Up to the age of twelve she had frequent *bilious attacks*, with vomiting of bitter stuff, lasting up to three days. Never colic or nose-bleed. The jaundice is increased by late hours and fatigue, and she gave up going to dances for this reason. It becomes more marked in hot weather. For some years she has been pale. Lately her joints are stiff, but limber up with exercise. (Stiffness probably muscular). She often has a feeling of lassitude. Otherwise she is well, except for an abnormal appetite; she does not feel satiated after a hearty meal (bulimia). The bowels usually move twice a day.

Physical Examination. Rather slender girl, but well developed and nourished. The slight tinge of yellow in the skin is rather becoming. The conjunctivæ appear more yellow than the skin. The heart is not enlarged; there is a soft systolic murmur in the pulmonary area. Pulse, 84. *Spleen:* Readily palpable, about 2 cm., below the ribs. *Liver:* Not enlarged. *Blood:* The serum gives a strong reaction for bilirubin. Red cells, 3,564,000. Hemoglobin, 70 per cent. (Sahli). Color index, 1. Leukocytes, 6600. Anisocytosis present, the average diameter of the red cells decreased (6.22 microns). No nucleated red cells. No poikilocytosis, polychromatophilia, or punctate basophilia; platelets normal. Differential count: Polynuclear neutrophiles, 74.75 per cent.; lymphocytes, 20.25 per cent.; mononuclears and transitionals, 3.75 per cent.; eosinophiles, 0.75 per cent.: mast cells, 0.5 per cent. *Urine:* Reddish yellow, no bile or urobilin, urobilinogen present in traces. Indican normal. Slightest possible trace of albumin, but no casts or blood. *Feces:* Soft, greenish yellow, acid. Microscopically there is an excess of neutral fat, with a few calcium soap crystals, but no excess of starch or muscle. Intense reaction for urobilin, considerable bilirubin.

Family IV. At least three members affected in three generations, probably several others. (Investigated through the kindness of Drs. N. A. Ludington and George Blumer, of New Haven).

CASE XI.—J. T., aged fifty-nine and one-half years, male, second child, of Scotch parents. *Family history:* His father, who died at seventy, of pneumonia, suffered from frequent attacks of vomiting of bile, lasting about a day; it is probable that his skin was yellow. Four brothers and one sister lived to grow up; one of the brothers was yellow at times, and probably had the "bilious attacks." A son of this brother is said to be sallow. The patient married his first cousin on the father's side; she is sallow and has pain in

the left side of the abdomen. She refused to be examined. Four children resulted from this marriage—two daughters who died in infancy, a son who is jaundiced (Case XII), and another son who is thought to be sallow. The patient's mother had severe arsenical poisoning while pregnant with him. *Past history:* The jaundice probably dates back to early manhood, when he began to have attacks of vomiting of bile, with headache, some pain in the right hypochondrium, and a decidedly yellow color of the skin. These attacks last two or three days, and are associated with an increase of the constipation to which he is subject. He frequently has urticaria, and used to have nose-bleed as a boy. Obstruction of the bowels at the age of twenty-two. Two years later had lead colic (occupation then, rubber-cutter.) For fifteen years he has had attacks of pain in the one or the other great toe, coming on suddenly at night. He has been a hearty eater of meat, and a beer drinker.

Physical Examination. Medium build, well developed, fairly nourished. Skin yellowish; face of a sallow, leathery color; conjunctivæ distinctly yellow. No lead line. The lungs show signs of emphysema. The heart is moderately enlarged to the left, with soft systolic murmurs at the apex and at the aortic area. Aortic second sound rather sharp. Subclavian arteries thickened, radials not. Pulse, 80; systolic pressure, 165 to 170. *Spleen:* Greatly enlarged, measuring 12 by 17 cm., not tender. Liver flatness from fifth rib to costal margin, where the edge of the organ is palpable. Distinct thickening about metatarsophalangeal joints of both great toes. No tophi. *Blood:* Red cells 2,804,000. Hemoglobin, 50 per cent. (Tallqvist). Color index, 0.9. Leukocytes, 7900. Moderate anisocytosis, average diameter normal (7.64 microns). No nucleated red cells. No achromia, poikilocytosis, polychromatophilia, or basophilia. Differential count: Polynuclear neutrophiles, 80.6 per cent., lymphocytes, 15.7 per cent.; mononuclears and transitionals, 2 per cent.; eosinophiles, 1.7 per cent. Urine of normal color; specific gravity, 1009; albumin, a slight trace; no bile or urobilin; a faint trace of urobilinogen present. Indican normal. In the sediment fairly numerous hyaline casts; no blood (chronic interstitial nephritis).

The complication with gout is of interest, but in the presence of lead poisoning and the overconsumption of meat and malt liquors is not surprising.

Case XII.—G. T., aged thirty-two years, son of J. T. The permanent yellow color was not noticed until ten years ago, but was probably present before that. Since the age of seventeen he has had *"bilious attacks,"* in which he would feel tired, drowsy, and depressed, with jaundice, constipation, and headache, and toward the close of the attack vomiting of bile, or *nose-bleed.* Several such attacks in a year, lasting a day or two. They seem to be brought on by constipation, fatigue, or irregular hours of eating. Light attacks without vomiting once every two weeks. When twenty years old

had a severe cramp in the epigastrium, doubling him up, and occasionally since then he has had similar attacks. (*Cholelithiasis.*) He has *hives* frequently, to which an occasional itching of the legs may be attributed. Appetite good, sleeps "unusually well." Stools always dark, "like chocolate." He is said to have had malaria eleven years ago, but had no chills; at that time a doctor found the spleen enlarged. Two months ago a prominent European consultant made a diagnosis of Banti's disease.

Physical Examination. Medium-sized man, sparely nourished. The skin of the body is a pale lemon-yellow, while the face is of a peculiar brownish-yellow, leathery color, unlike the hue of ordinary jaundice. The conjunctivæ are distinctly jaundiced. Heart not enlarged, slight systolic murmur at base. Pulse normal. *Spleen:* Greatly enlarged, measuring 22 x 13 cm., reaching below to the level of the spine of the ilium and to the middle line at the navel. It is smooth and hard, and tender at one point. *Liver:* Palpable at costal margin, area of dulness normal. *Blood:* Serum strongly tinged with bile, and gives a marked Hedenius reaction. Red cells, 3,492,000. Hemoglobin, 65 per cent. (Tallqvist). Color index, 0.9. Leukocytes, 5800. Two normoblasts seen. Marked anisocytosis, average diameter decreased (6.48 microns). No achromia, slight poikilocytosis, some polychromatophilia, no punctuate basophilia, except in one normoblast. Platelets normal. Differential count normal. *Urine:* Orange, contains urobilin and urobilinogen, but no bile. *Feces:* Mushy, yellow (milk diet), alkaline. Numerous hreds resembling connective tissue. Microscopically normal except for increase in the calcium soap crystals. Urobilin strongly positive, bilirubin absent.

Stomach examination after Ewald breakfast: 40 c.c. undigested bread mixed with mucus, free HCl 0, total acidity 5, slight test for lactic acid (chronic gastritis).

Case XIII.—C. T., aged seven years, son of the foregoing patient, grandson of J. T. The eyes have been yellowish since birth. The color becomes more apparent when he is constipated. He has had no children's diseases, only frequent colds. Nose-bleed once, never colic or vomiting attacks, except after eating strawberries or bananas. Hives frequently. The child has seemed healthy, but never could run like the other boys, and complains of a pain in the left side of the abdomen after exercise. Appetite and digestion good, bowels regular as a rule, sometimes constipated.

Physical Examination: March, 1910. Well developed for his age, and well nourished. He is the least jaundiced of this family, but the skin and conjunctivæ are distinctly though faintly yellow. On the legs, arms, and scrotum a few wheals, one on the scrotum showing hemorrhagic infiltration. Mucous membranes somewhat pale. Heart not enlarged, loud systolic murmur in pulmonary area and venous hum in neck, pulmonic second sound not accentuated.

Spleen: Much enlarged, measuring 18 by 13 cm., smooth, not tender. *Liver:* Slightly enlarged; dulness above at sixth rib; liver palpable 3 cm. below costal margin. *Blood:* The serum on standing shows a green fluorescence and is strongly positive for bile pigment. Red cells, 3,412,000. Hemoglobin, 50 per cent. (Sahli). Color index, 0.74. Leukocytes, 8500. Two normoblasts and one "intermediate" megaloblast seen. Marked anisocytosis, average diameter decreased (6.69 microns). Considerable achromia and poikilocytosis, some polychromatophilia, and very fine punctate basophilia. *Urine:* Somewhat high colored, no bile, urobilinogen absent, urobilin in traces. Indican normal. *Feces:* Formed, dry, yellowish brown, alkaline, microscopically normal. Urobilin present, but reaction with zinc acetate less intense than in the other cases. Bilirubin absent.

An interesting point in this family is the tendency to urticaria, which is present in all three generations.

The bibliography which follows makes no pretence at completeness. Only those articles are included which could be personally verified, hence some foreign references have been omitted. The French literature on the subject is very voluminous, owing to the fact that the same case may be reported twice by different observers, and that some authors feel it necessary to write many articles on the subject. Many such references are purposely omitted.

Bibliography.

Chronic Family Jaundice, Including the Acquired Form.

P. Abrami. Bull. et mém. Soc. méd. d. hôp de Paris, 1908, xxvi, 329.
J. A. Arkwright. Edinburgh Med. Jour., 1903, xiii, 52.
T. Barlow and H. B. Shaw. Trans. Clin. Soc. London, 1902, xxxv, 155; also Med. Press and Circular, 1902, lxxiii, 564.
E. Benjamin and E. Sluka. Berl. klin. Woch., 1907, xliv, 1065.
Bettmann. Münch. med. Woch., 1900, xlvii, 791.
Blum. Abstract in Deut. med. Woch., 1909, xxxv, 1773.
A. Cade. Bull. et mém Soc. méd. d. hôp. de Paris, 1908, xxvi, 421.
A. Cade and J. Chalier. Lyon méd., 1908, cxi, 930.
A. Campani and G. Ferrari. Clin. Med. Ital., 1908, xlvii, 394.
R. Carporali. Med. Ital., Napoli, 1905, iii, 373.
A. Chauffard. Bull et mém Soc. méd. d. hôp de Paris, 1901, xviii, 444.
A. Chauffard. Semaine méd. Paris, 1907, xxvii, 25.
A. Chauffard. Ibid., 1908, xxviii, 49.
A. Chauffard and N. Fiessinger. Bull et mém. Soc. méd. d. hôp de Paris, 1907, xxiv, 1169.
Claus and Kalberlah. Berl. klin. Woch., 1906, xliii, 1471.
Gandy and Brûlé. Bull et mém. Soc. méd. d. hôp de Paris, 1909, xxviii, 369.
A. Gilbert, J. Castaigne, and P. Lereboullet. Bull et mém Soc. méd. d. hôp de Paris, 1900, xvii, 948.
A. Gilbert and P. Lereboullet. Ibid., 1903, xx, 385.
H. P. Hawkins and L. S. Dudgeon. Quart. Jour. Med., 1909, ii, 165.
G. Hayem. Presse méd., 1898, i, 121.
G. Hayem. Bull. et mém. Soc. méd. d. hôp de Paris, 1908, xxv, 122.
R. Hutchison. (Further report on Murchison's family.) Clin. Jour., London, 1909, xxxiv, 241.

R. Hutchison and P. N. Panton. (Same cases as in foregoing article.) Quart. Jour. Med., 1909, ii, 432.
Jacob and Levy-Valensi. Bull et mém. Soc. méd. d. hôp. de Paris, 1909, xxvi, 219.
H. v. Krannhals. Deut. Arch. f. klin. Med., 1904, lxxxi, 596.
P. Le Gendre. Bull. et mém. Soc. méd. d. hôp de Paris, 1897, xiv, 457.
P. Le Gendre and M. Brulé. Bull et mém. Soc. méd. d. hôp. de Paris, 1909, xxvi, 112.
Lesné and Ravaut. (Experimental work.) Soc. de biologie, 1901, 1106.
L. Lortat-Jacob and G. Sabaréanu. Rev. de méd., 1904, xxiv, 810.
H. A. Mason. Quart. Med. Jour., Sheffield, 1902, xi, 40.
O. Minkowski. Verhandl d. Cong. f. inn. Med., 1900, xviii, 316.
S. Möller. Berl. klin. Woch., 1908, xlv, 1639.
C. Murchison. Diseases of the Liver, third edition, 1885, 481.
W. Oettinger. Bull et mém. Soc. méd. d. hôp de Paris, 1908, xxvi, 391.
G. Péju. Loire méd., 1908, xxvii, 117.
A. Pick. Wien. klin. Woch., 1903, xvi, 493.
A. Plehn. Deut. med. Woch., 1909, xxxv, 1749.
R. Pollak. Wien. med. Woch., 1908, lviii, 1489.
F. J. Poynton. Lancet, 1910, i, 153.
E. Renaux. Presse méd. Belge, 1909, lxi, 711.
W. Starkiewics. Rev de méd., 1909, xxix, 61.
K. v. Stejskal. Wien. klin. Woch., 1909, xxii, 661.
H. Strauss. Berl. klin. Woch., 1906, xliii, 1590.
H. Strauss. Ibid., 1908, xlv, 1643.
H. Vaques and Giroux. Bull et mém. Soc. méd. d. hôp. de Paris, 1907, xxiv, 1184.
F. P. Weber. (Acquired case.) Amer. Jour. Med. Sci., 1909, cxxxviii, 24.
F. P. Weber and G. Dorner. Lancet, 1910, i, 227.
F. Widal and P. Ravaut. Bull et mém. Soc. méd. d. hôp de Paris, 1902, xix, 984.
F. Widal, P. Abrami, and M. Brûlé. Presse méd., 1907, xv, 641.
Widal, Abrami, and Brûlé. (Experimental work.) Bull et mém Soc. méd. d. hôp. de Paris, 1907, xxiv, 1354.
C. Wilson. Trans. Clin. Soc. London, 1890, xxiii, 162.
C. Wilson and D. Stanley. Trans. Clin. Soc. London, 1893, xxvi, 163.

Chronic Jaundice with Erythrocytosis.

Guinon, Rist, and Simon. Bull et mém Soc. méd. d. hôp de Paris, 1904, xxi, 786.
M. Mosse. Deut. med. Woch., 1907, xxxiii, 2175.

Fatal Icterus Neonatorum without Obstruction of the Bile Ducts.

G. A. Auden. St. Barth. Hosp. Rep., 1905, xli, 139.
J. Busfield. Brit. Med. Jour., 1906, i, 20.
J. A. Arkwright. Edinburgh Med. Jour., 1902, xii, 156.
Ashby and Wright. Diseases of Children, Fifth Edition, 1905, 29.
R. Beneke. Münch. Med. Woch., 1907, liv, 2023.
J. E. Blomfield. Brit. Med. Jour., 1901, i, 1142.
P. Esch. Zentralbl. f. Gyn., 1908, xxxii, 969.
L. Lagrèze. Beiträge z. Geburtsh. u. Gyn., 1906, x, 57.
J. Pfannenstiel. Münch. Med. Woch., 1908, lv, 2169, 2233.
Schmorl. Verhandl. d. Deutsch. path. Gesellsch, 1903, vi, 109.

Familial Splenomegaly, Gaucher's Type

W. Risel. Beiträge z. path. Anat., 1909 xlvi, 241.
F. Schlagenhaufer. Virchow's Archiv, 1907, clxxxvii, 125.
(These two articles contain good bibliographies.)
Marchand. Münch. med. Woch., 1907, liv, 1102.

A STUDY OF MURMURS IN PULMONARY TUBERCULOSIS.

By Charles M. Montgomery, M.D.,

PHYSICIAN TO THE PHIPPS INSTITUTE FOR THE STUDY, TREATMENT, AND PREVENTION OF TUBERCULOSIS; PHYSICIAN TO THE PHILADELPHIA HOME FOR CONSUMPTIVES, CHESTNUT HILL, PHILADELPHIA.

Two things in particular prompted the present study in regard to murmurs: (1) Their frequency and wide distribution in pulmonary tuberculosis, especially in far advanced cases; and (2) the difficulties in diagnosis they may occasion. The clinical records in a number of cases of pulmonary tuberculosis have been investigated in regard to murmurs, and the results tabulated. The term murmur has been used in the restricted sense of a sound possessing more or less of a blowing or whiff-like character, and not in the comprehensive sense, which "includes all those adventitious acoustic phenomena connected in some way with the heart's action, and not resembling in tone the normal cardiac sounds" (Babcock).

The cases have been divided into two groups: (1) Those in which there is some gross lesion of the heart or bloodvessels—for instance, endocarditis or myocarditis; and (2) those without any such lesion definitely diagnosticated, and usually without any clearly defined cause. The second group will be considered first. All cases are to be understood as belonging to this second group except when the contrary is specifically stated.

Murmurs independent of demonstrable changes in the heart or bloodvessels occurring in tuberculosis have received attention from time to time since Stokes described a murmur in the subclavian artery. Some authors, for instance, Walshe, Wilson Fox, and Samuel West, devote a small space to these murmurs; others, as Cornet, barely refer to them. From the opinions expressed one concludes that murmurs of this sort are not limited to tuberculosis, in fact, may occur in normal individuals; that they are heard rather infrequently; that they are apt to be temporary and to be modified by the phases of respiration; and that their causes cannot be definitely determined. These murmurs are usually described as occurring most frequently at the base of the heart or in the subclavicular regions, less often at the apex, over the back, and elsewhere.

Uniform statistics on the frequency and distribution of murmurs are not to be expected because of the variable factors on which murmurs often depend. Some of these factors are exertion, sudden or protracted, the position of the patient, the character of the breathing, the stage of the disease, the frequency of examination, the quietness of the examining room (a very important factor in hearing the fainter murmurs), the natural acuity and the training of the examiner's ear, and the degree of concentration employed in ausculting. Statistics on the frequency of murmurs in pulmonary

tuberculosis are available from comparatively few sources. At the Henry Phipps Institute[1] functional murmurs occurred in 3.4 per cent. of 2078 cases, distributed as follows: Systolic at the mitral area, 36 (1.73 per cent.), and systolic at the pulmonic area, 35 (1.67 per cent.). At the Adirondack Cottage Sanitarium,[2] where most of the cases are not far advanced, functional murmurs occurred in 6 per cent. of 1289 cases. These murmurs were divided about equally between the base (chiefly the pulmonic area) and the apex.

The occurrence of murmurs over the chest was investigated in 80 cases of pulmonary tuberculosis, in which it was impossible to ascribe the cause to any gross cardiac or vascular disease. The great majority were females—63, in contrast to 17 males. There was 1 case under ten years of age, there were 9 cases between ten and twenty years, 38 between twenty and thirty years, 18 between thirty and forty years, 7 between forty and fifty years, and 7 cases were over fifty years of age. In other words, there was nothing specially interesting about their ages. Most of the cases were far advanced —61, in contrast to 9 incipient and 10 moderately advanced cases. Examinations were made repeatedly in most of the cases, and were usually conducted in an absolutely quiet room.

FREQUENCY AND DISTRIBUTION OF THORACIC MURMURS IN 80 CASES (NOT DUE TO DEMONSTRABLE CARDIAC OR VASCULAR DISEASE).

	Cases.
Murmurs present	56
Both anteriorly and posteriorly	25
Anteriorly	22
Posteriorly	9
Murmurs anteriorly	43
Both sides	17
Right side	7
Left side	19
Murmurs on the right side, anteriorly	23
Both above and below third rib	12
Above third rib	8
Below third rib	3
Murmurs on the left side, anteriorly	36
Both above and below third rib	21
Above third rib	6
Below third rib	9
Murmurs in the axilla	10
Both axillæ	1
Right axilla	4
Left axilla	5
Murmurs posteriorly	34
Both sides	8
Right side	11
Left side	15

[1] Henry Phipps Institute, Fifth Annual Report.

[2] Lawrason Brown, AMER. JOUR. MED. SCI., December, 1908.

THE FREQUENCY AND DISTRIBUTION OF THE MURMURS. Murmurs were audible over the chest in 56 of these 80 cases. According to the stage of the disease, murmurs were present in 3 of the 9 incipient cases, 8 of the 10 moderately advanced cases, and 45 of the 61 far advanced cases. Murmurs were audible both anteriorly and posteriorly in 25 cases, anteriorly alone in 22 cases, posteriorly alone in 9 cases. Anteriorly, murmurs were present on both sides of the chest in 17 cases, on the right side alone in 7 cases, and on the left side alone in 19 cases. Over the sternum, murmurs were recorded in 24 cases. On the right side of the chest, in front, murmurs were present both above and below the third rib in 12 cases, only above the third rib in 8, and below in 3 cases. On the left side, in front, murmurs occurred both above and below the third rib in 21 cases, only above the third rib in 6, and below the third rib in 9 cases. Murmurs anteriorly were audible in the different interspaces in the following number of cases:

	Right side. Cases.	Left side. Cases.	Sternum. Cases.
First interspace	10	12	5
Second interspace	20	26	13
Third interspace	13	20	14
Fourth interspace	7	19	12
Fifth interspace	5	18	9
Below fifth interspace	1	1	2
Not stated	0	0	1

Posteriorly, murmurs were present on both sides in 8 cases, on the right side alone in 11 cases, on the left side alone in 15 cases. Murmurs were heard in both axillæ in 1 case, in the right axilla alone in 4 cases, and in the left axilla alone in 5 cases. In all the cases in which the murmur was audible in the axilla one could also be heard in some other part of the chest, and usually the axillary murmurs were topographically continuous with those audible elsewhere.

For practical purposes, many of the murmurs may be advantageously classified according to limited areas over which they are heard with the greatest intensity; for example, the base of the heart, the region of the apex, the region of the angle of the scapula, etc. Some murmurs, however, do not have any very limited area of maximum intensity.

In my experience, murmurs over the front of the chest occur most frequently at the base. They are generally heard in the second interspace, more often in the left than the right, or at the same level over the sternum. Laterally, they usually extend only a short distance from the sternum, particularly on the right side. Murmurs at the base may have a wider distribution, but under these circumstances it is often difficult to determine whether we are dealing with two or more murmurs running together or overlapping. In 37 of the 80 cases a murmur was audible in the right or left second

interspace, or at a corresponding level over the sternum, most of these covering quite limited areas.

Murmurs were heard about half as often at the apex as at the base. Their maximum intensity was at, or a little inside, the cardiac apex, usually in the fifth interspace, between the parasternal and midclavicular lines; less often in the fourth interspace. They were rarely transmitted beyond the anterior axillary line, even when they seemed pretty clearly due to mitral regurgitation (mitral regurgitation not dependent on gross cardiac disease). In 4 of these cases the situation, transmission, loudness, and persistency of these murmurs seemed to indicate leakage at the mitral valve.

Systolic murmurs over the sternum, below the level of the fourth rib, occurred in 13 cases. They were usually faint, and sometimes were transmitted from other regions. Sufficient evidences on which to base a diagnosis of tricuspid regurgitation, particularly the presence of a positive venous pulse, were lacking in all the cases. In only 1 case was anything heard suggestive of the xiphosternal crunching sound.

The murmurs on the left side, anteriorly, covered larger areas, as a rule, than those on the right side. Out of 36 cases with murmurs on the left side, the murmurs were limited to a single interspace (usually the second or the fifth) in 13 cases, to two interspaces in 6 cases, to three interspaces in 5 cases, to four interspaces in 5 cases, to five interspaces in 6 cases, and to six interspaces in 1 case. In no case was a murmur limited to the axilla. Apical murmurs were transmitted to the axilla in 3 out of 6 cases with axillary murmurs.

Posteriorly, murmurs were recorded in 34 of the 80 cases, eight times on both sides, eleven times on the right side alone, and fifteen times on the left side alone. A murmur may be heard over a very limited area or over the whole of the back of the chest. While the latter is rare, it is common to find a murmur covering a considerable portion of one or both sides of the back. But in nearly every case, irrespective of the extent of the murmur, an area of maximum intensity will be found at or near the angle of the scapula, close to the angle of the scapula or below it, or inside it, or over the lower portion of the interscapular region. In only 1 case were two points of special intensification recorded on one side, posteriorly—a case in which the murmur was audible all over the left side, posteriorly, but specially marked above the spine of the scapula and at the angle of the scapula.

Murmurs may occur over very limited or over extensive areas. In 1 incipient case a murmur could at times be heard over nearly the entire chest. Murmurs entirely distinct from one another may be heard in different parts of the chest in the same individual as at the base and at the apex, or may blend together and prevent outlining the exact limits of a murmur.

Only murmurs over the chest have been referred to. Adventitious sounds above the clavicles are not infrequent in tuberculosis; sometimes they are murmurs of a blowing or whiff-like character, but more often only a roaring, humming, or rumbling sound is heard.

TIME OF THE MURMURS. Systolic murmurs were present in all of these 56 cases. It was sometimes impossible to tell with absolute certainty the time of the murmurs over the back of the chest. Out of the 56 cases, a diastolic murmur was recorded in only 4, and in 2 of these cases only once after several examinations. All the diastolic murmurs were associated with systolic murmurs, and were of the same character. In 3 of the cases the murmur occurred over some part of the sternum and the left side adjacent, and in 1 the murmur was audible on the right side from the second to the fifth interspace, inclusive, and from the sternum to the midclavicular line, and very faintly for a short distance beyond. The last occurred only on inspiration. In 1 of these cases at one examination there could at times be heard a faint diastolic murmur in the left interscapular region. In 3 of the cases the murmur was rough. In all the cases the second aortic sound was, at least at times, accentuated.

In a case not included in the above series a very extensive diastolic murmur, not dependent on any demonstrable cardiac or vascular disease, was encountered in a woman, aged twenty-eight years, with extensive left-sided pulmonary and pleural involvement, the heart being apparently slightly retracted upward and to the left. Her hemoglobin was 80 per cent. The diastolic murmur was audible over the sternum from the second interspace to the sixth rib, and extended beyond the left midclavicular line, reaching the anterior axillary line at the level of the fifth rib. The maximum intensity was in the third interspace, at the parasternal line. There was also audible a systolic murmur over a part of this area and over a part of the right side. The time and distribution of murmurs varied on different occasions.

INTENSITY OF THE MURMURS. Faint murmurs were described in 33 out of 48 cases in which the intensity of the murmurs was mentioned. Sometimes they were very faint, an occasional one being audible only with a Bowles stethoscope. In 1 case, a murmur could be heard with an ordinary stethoscope and not with the Bowles. To hear some of these murmurs, absolute quiet in the room and concentrated attention were necessary. In some patients murmurs could be heard on only one of several examinations, and sometimes specially favorable circumstances, as a certain position of the patient, excitement, exertion, etc., were required.

In 15 cases a murmur was described as distinct, fairly loud, loud, or marked. In 4 cases there was quite a marked systolic murmur at the apex. The base, the apex, and the regions of the angles of the scapulæ were the most common seats of the louder murmurs and of the maximum intensity of murmurs of wide distribution.

Fairly loud murmurs, as a rule, covered only small areas, but were more apt to be extensive posteriorly than anteriorly. Various factors, like exertion, that may produce murmurs, may also increase their intensity. The different phases of the respiratory act may have quite a marked effect on the loudness of a murmur. Like murmurs due to endocarditis, these murmurs may vary greatly at different examinations.

Length or Duration of the Murmurs. The length of the murmurs was shorter than often occurs with murmurs due to other causes, like endocarditis, but the rate of the heart was nearly always increased. The only case in which a fairly prolonged murmur was recorded was an incipient case, with a normal heart rate.

The Quality of the Murmurs. The murmurs were generally soft and blowing in character, sometimes being heard as very faint whiffs. Occasionally a slightly ringing quality was audible. In only 3 cases was a rough murmur recorded, in 2 cases the roughness affecting both the systolic and the diastolic murmurs. Rough murmurs were audible only anteriorly.

While murmurs in advanced cases may vary from time to time in loudness, extent, etc., they usually do not entirely disappear, and when they do it is generally only temporarily. This persistency we have noticed especially in regard to murmurs at the apex and over the back.

Relation to Respiration. In 36 cases the relations of the murmur to inspiration, expiration, and the respiratory pause were recorded. While most of the murmurs could be heard during all parts of the respiratory act, they were usually louder at one portion than at another. The commonest time for diminution or cessation of murmurs was during inspiration, except at the very end of inspiration. In 10 cases the murmur was inaudible during inspiration. In but 1 case a murmur was stated to have been heard during inspiration only. When murmurs were modified by respiration the greatest intensity usually took place during expiration, or during expiration and the respiratory pause, sometimes at the end of inspiration and beginning of expiration.

The effect of holding the breath was recorded in 16 cases with murmurs. In only 2 cases did the murmur disappear when breathing was suspended. As a rule, the murmurs were heard equally as plainly when the breath was held as during the act of respiration. In 2 cases a murmur could only be heard when breathing was suspended; in 1 of these cases only after expiration. Occasionally a murmur would weaken after the breath had been held for some time.

The relative weakness or absence of murmurs during inspiration in many of the cases, I believe, was often due to the loudness and sometimes to the exaggeration of inspiration. Inspiration is normally louder than expiration, and is apt to become intensified over

healthy tissue when such tissue is reduced in amount. Thus, murmurs are apt to be heard over one base at the back when the opposite side is extensively infiltrated, and the loudness of inspiration under such circumstances is quite sufficient to obscure a faint murmur.

In only 3 cases did the character of the murmurs suggest that they might be due to the passage of air through normal or abnormal channels, instead of their being circulatory in origin. Such murmurs may have been caused oftener, but we could not demonstrate this. Rarely distinct respiratory puffs, synchronous with the heart beat, occurred. Occasionally it may be difficult to distinguish between a murmur and a rale.

Relation to Bodily Position. Most of the 80 cases were examined in a sitting position during the ordinary routine chest examination, but a small proportion were also auscultated while standing or while lying down. Occasionally the position of a patient modified the murmur, but it was generally less the position than the attending exertion that seemed responsible for the modification. In advanced tuberculosis it takes very little effort to cause or to modify murmurs. Sometimes one position will reveal a faint murmur; the same position later, after the patient has been listened to in various other positions, may reveal a much louder murmur. Or the reverse result may be observed. For instance, a murmur audible just after a patient takes his seat, may disappear after this position has been maintained for some time. With the murmurs at the apex, the sitting position was more apt to be associated with the presence of a murmur or its intensification than the horizontal position. Very few records were made of examinations with the patients in the right or left lateral positions.

Relation of Murmurs to the Kind of Underlying Lung Tissue, Whether Healthy or Diseased. In advanced tuberculosis, murmurs are usually louder or more widespread, and occur oftener over the functionating lung tissue than over the diseased portions, with the possible exception of the left side in front. Thus, in 10 cases with a murmur on the left side posteriorly, and none on the right, there was considerable healthy tissue on the left side, especially at the base, and much less or none at all on the right side. Likewise, in 8 cases with a murmur at the right base posteriorly, more healthy tissue was found here than at the corresponding situation on the left side. In a boy, aged two years, a murmur was audible over the right back when the left side was extensively diseased. Murmurs were also more frequent over the right side, in front, when the tissue here was healthy than when it was diseased. When there was not much lung involvement on either side, however, murmurs were more frequent or were louder or more widespread at the left base posteriorly, than at the right, in our cases in the proportion of 6 cases on the left to 1 case on the right—an occurrence not peculiar to tuberculosis.

ETIOLOGY. The attempt to determine the causes of these murmurs in any given case is usually met with great difficulties. Any factor proposed to explain their occurrence will often be wanting in cases with murmurs, or may be present even when murmurs are absent. Even in cases in which murmurs can be produced artificially, for instance, through exertion, one can, as a rule, only venture an opinion as to their complete etiology. The subject is further complicated by the occurrence of murmurs in apparently normal individuals.

Murmurs associated with tuberculosis and with other forms of marked debility probably often depend on similar causes, the exact nature of which, however, is usually obscure. The determining cause in some of the cases is doubtless contraction or imperfect expansion of the great vessels, resulting from adhesions, enlarged glands, pulmonary consolidation, displacement of the heart, and an enlarged heart pressing on bloodvessels. According to Thayer and MacCallum,[3] only very slight pressure over the pulmonary artery or conus arteriosus, in dogs, results in the development of a systolic thrill and murmur immediately beyond the point of pressure. If murmurs in the pulmonary artery are produced as easily, relatively, in man as in dogs, traction or pressure upon this vessel may readily explain some of the murmurs audible at the base of the heart. Some of the murmurs may be ascribed to roughening of the aorta or to slight roughening or thickening of the valves of the heart. The frequency of the latter condition is shown by the figures of Norris,[4] who found endocardial thickening in 15 per cent. of 1764 autopsies on tuberculous patients, the proportion of valvular involvement being: mitral, 183; aortic, 126; tricuspid, 23; and pulmonary, 13. A congenitally small aorta, said to be not infrequent in tuberculosis, suggests a possible cause for some of the murmurs. West considers that the murmurs at the angle of the scapula may often be due to air being forced out of lung tissue by the cardiac pulsations. It seems possible that murmurs audible over a large part of one healthy lung when the opposite lung is extensively involved may be due to circulatory changes in the pulmonary artery on the unaffected side. The marked persistent murmurs at or near the apex are probably quite often due to leakage at the mitral valve, the result of weakness of the mitral sphincter or the papillary muscles. Similar conditions affecting the tricuspid valve may cause some of the murmurs heard in the lower sternal region. A moderate oligochromemia occurs frequently in tuberculosis, not oftener, however, in cases with murmurs than in those without. We have been unable to demonstrate any constant relationship between the transmission of murmurs and pulmonary consolidation near their seat of origin. In many cases

[3] AMER. JOUR. MED. SCI., February, 1907.
[4] Ibid., October, 1904.

on such relationship exists, and in some, especially those with murmurs situated posteriorly, consolidation seems to interfere with their transmission. The proportion of cases with murmurs increases with the advance in the disease, and for their explanation one naturally looks to the conditions peculiar to advanced cases, particularly as they affect the circulatory system. Some of these conditions are quite constant, for instance, an increase in the pulse rate and a fall in blood pressure; others are more variable, like the strength of the heart beat. But it is impossible to find any relationship between these circulatory conditions and the occurrence of murmurs constant enough to warrant definite conclusions as to causation; and, least of all, is it possible to demonstrate any etiological relationship in individual cases. It is not surprising that slight exertion or excitement produces or modifies murmurs in weak advanced cases in which various circulatory factors, for instance, the rate of the heart, are so easily upset by even trivial causes.

In the maze of questions brought up by this subject one would fain take comfort in what has been said by Sahli, that the difficult problem is not to explain why murmurs do sometimes occur, but rather why, with all the conditions apparently favorable for their production, they do not always occur.

Diagnosis. A diagnosis as to whether a murmur is due to endocarditis or to other causes may be made very difficult, even impossible, by the presence of advanced pulmonary tuberculosis. Such difficulties have been most frequently occasioned, in our experience, by systolic murmurs at the apex. With these apical murmurs we have to determine whether mitral regurgitation is present or absent, and, if regurgitation is present, to determine whether it is due to endocarditis or not.

In advanced cases of pulmonary tuberculosis with presumable cardiac weakness, fairly loud systolic murmurs at or near the apex, transmitted toward the axilla, and heard repeatedly over a considerable length of time, may, in the majority of cases, be strongly suspected of being due to leakage at the mitral valve. These murmurs are usually only faintly transmitted beyond the midclavicular line, and are rarely audible in the axilla. They are unaccompanied by demonstrable enlargement of the heart, or by any apparent general effect, and are interesting chiefly for the uncertainty in diagnosis they may occasion.

Difficulty in determining whether a murmur, supposedly due to mitral regurgitation, occurring in advanced pulmonary tuberculosis, is due to endocarditis or not may arise because tuberculosis and heart disease have so many manifestations in common. Cyanosis, dyspnœa, curving of the nails, accentuation of the second sound at the pulmonary cartilage, a murmur at the angle of the scapula, are common in both heart disease and pulmonary tuberculosis. The effect of position on the murmur has been too variable, in our

experience, to be of much real help. The all-important evidence, that a mitral regurgitant murmur is due to endocarditis, namely, enlargement of the heart, may be difficult to obtain in tuberculosis because of the difficulty to locate the position of the apex, and to determine the cardiac outlines by percussion. Uncertainty as to the location of the apex may be due to a very feeble apex beat, or to a diffuse one dependent on an overacting heart. The location of the apex and the percussion outlines may give unreliable information, on account of the presence of compensatory emphysema, retraction of the lung, consolidation adjacent to the heart, and cardiac displacement. However, when the heart is drawn to the left, the maximum apex impulse is frequently in the fourth interspace, and in no case do we recall a maximum apex impulse to have occurred downward (sixth or seventh interspace) and outward in a heart itself normal.

A definite history of acute articular rheumatism furnishes corroborative evidence in favor of endocarditis, while a history simply of rheumatic pains is of little value, as they occur so frequently in tuberculosis.

With the appearance of failing compensation the peculiar features of this condition should be sought for, as they are apt to furnish quite a contrast to what is encountered in tuberculosis. Marked pulsation and dilatation of the cervical vessels is common in the later stages of heart disease, but is uncommon even in advanced tuberculosis, except for the prominence of the veins that may be seen during the act of violent coughing. Cyanosis is often more pronounced in failing compensation than in advanced tuberculosis. Pulsation from an enlarged liver is frequently met with in the final stages of failing compensation, an unknown occurrence, in our experience, in uncomplicated tuberculosis. On account of the great rarity of the typical evidences of failing compensation in cases very far advanced in tuberculosis, if, indeed, they ever appear under these circumstances, their occurrence furnishes evidence of the strongest kind in favor of the presence of some causative condition in no way associated with tuberculosis.

Myocarditis due to valvular disease and various causes of a non-tuberculous nature often exhibits certain features that are uncommon in cases of tuberculosis even when they are advanced. Thus, marked irregularities may occur within a short period in the force of the heart beats, or in the duration of individual cardiac cycles. A typical example is a case in which the heart beats weaken at irregular intervals, and are accompanied by a corresponding intermission of the pulse. Another example is found in cases with delirium cordis. These abnormalities, moreover, do not necessarily follow any regular sequence or depend on any temporary or removable cause. In tuberculosis, on the other hand, the irregularities are apt to be limited to variations in rate, or to the

interpolation of additional sounds, such as occur in reduplications, the cardiac rhythm, as a whole, not being affected. Sudden and marked variations in rate are frequently met with in tuberculosis, but are often due to some temporary cause, like excitement, and disappear on its removal. In tuberculosis abnormal cardiac sounds are common, but the length of individual cardiac cycles and the force of the heart beats only rarely show marked and irregular variations. When these variations do occur they often depend on some temporary and removable cause. We refer, of course, to sounds during a limited time, for instance, during one examination, and not to variations that may occur from day to day or from week to week.

Other murmurs due to endocarditis or to congenital cardiac defects seem of less practical importance diagnostically than the mitral regurgitant murmurs, either because of their infrequency or because of the greater readiness with which a diagnosis may usually be made. Unlike mitral regurgitation, the other common forms of valvular disease, mitral stenosis, and aortic regurgitation have certain distinctive features, the former especially the peculiarity of the thrill and murmur, and the latter especially the evidences outside of the heart. Moreover, these features are not likely to be obscured by the associated tuberculosis.

Endocarditis was recorded in 0.9 per cent. of 71,000 cases of pulmonary tuberculosis collected by Lawrason Brown.[5] A positive diagnosis of endocarditis was made in 2 cases, and a probable diagnosis of endocarditis in 1 case, out of 171 consecutive cases of pulmonary tuberculosis at the Home for Consumptives at Chestnut Hill. There were 32 incipient, 44 moderately advanced, and 95 far advanced cases; 41 were males and 130 were females. Doubtful cases were examined repeatedly over considerable periods of time. No cases of pericarditis, of congenital cardiac defect, or of vascular disease other than arteriosclerosis were diagnosticated in this group of cases. Myocarditis was strongly suspected in a number of cases, particularly advanced ones, but I must admit that we have rarely been able to furnish scientific evidence of this condition in uncomplicated tuberculosis.

CASE I.—This patient is a young woman, aged twenty-seven years, single. Her occupation has been ordinary housework. At twelve years of age she had pneumonia, and since then her health has never been completely restored. At fifteen she had rheumatic pains in all her limbs. At sixteen she had measles, and the same year developed an anal fistula. At nineteen she had typhoid-fever and pleurisy: the latter recurred several times later. The duration of the tuberculosis is considered to have been between eight and fifteen years. Her height is five feet one and a half inches, and her weight

[5] AMER. JOUR. MED. SCI., February, 1909.

110 pounds. The sputum contained tubercle bacilli on the last examination. The urine contains no albumin. The hemoglobin is 75 per cent. The diagnosis of the pulmonary condition is arrested incipient tuberculosis.

Heart. The apex beat is usually diffuse, reaching beyond the left midclavicular line in the fourth and fifth interspaces. A presystolic thrill is usually present at the apex. Deep percussion gives dulness above at the second rib, on the right at the right border of the sternum, and on the left a short distance beyond the midclavicular line. The second pulmonic sound is at times accentuated. There is always present a prolonged presystolic sound, usually a rumble, sometimes a whiff-like murmur, over an area varying in size in the fourth and fifth left interspaces near or at the apex. Less often, there is a systolic murmur in the region of the apex, sometimes reaching as far as the anterior axillary line, promoted more by exertion than by position. The patient enjoys moderate, though not vigorous, health, except for occasional attacks of gastric disturbance, accompanied with marked palpitation and dyspnœa. At these times there may be marked arrhythmia of the heart, even a mild grade of delirium cordis, suggesting myocarditis, though, ordinarily, compensation is fairly well maintained.

Diagnosis. Endocarditis of the mitral valve, with mitral stenosis and, to a less extent, mitral regurgitation; moderate cardiac hypertrophy.

Case II.—M. C., female, aged fifteen years, single, has been attending school irregularly. She had a typical attack of acute articular rheumatism at six, and has never been as well since. Her history of tuberculosis dates back seven years, when she had an attack of pleurisy. She is five feet in height and weighs 90 pounds. There is no albumin in the urine, the hemoglobin is 88 per cent. The most extensive involvement is on the left side. While this is a far advanced case, the patient is steadily improving, and leads a pretty active life.

Heart. The apex beat is diffuse, the most marked impulse being in the left midclavicular line, in the fifth interspace. There are no thrills. The upper border of cardiac dulness is at the third rib, the right border at the right border of the sternum, and the left border a short distance beyond the midclavicular line in both the sitting and horizontal positions. The pulmonic second sound is accentuated. When the patient is sitting there is a constant, distinct, fairly loud, blowing systolic murmur, most marked in the fifth interspace at the midclavicular line, transmitted into the left axilla, audible to the right as far as the parasternal line, and disappearing above at the junction of the latter with the third rib. It is much fainter in the horizontal position. Faint systolic murmurs are audible at the inferior angle of the scapulæ, the more marked one on the left side.

Diagnosis. Endocarditis of the mitral valve, with mitral regurgitation; moderate cardiac hypertrophy; compensation good.

CASE III.—J. F. B., male, aged forty years, married, travelling salesman by occuaption, had nothing of importance in his family history, except that his maternal aunt had died twenty-five years before of consumption. He had scarlet fever at seven, but gave no history of rheumatism. His mother states that he began to have "spells," accompanied with unconsciousness, at twelve, and that he has always been a little odd. He stated that he had a heart attack at twenty, and that occasional attacks of fainting had occurred since. For a number of years he had been subject to copious hemorrhages from the bowels, and he had suffered from stomach trouble. Five months before admission he had had a violent cold, something like whooping cough, accompanied with severe dyspnœa, which had never left him. The duration of the tuberculosis had apparently been at least five months. His height was five feet six and one-half inches. His weight was 129 pounds, only 10 pounds loss in the previous five months, though twelve years previously he had weighed 154 pounds. The sputum showed tubercle bacilli before admission, none on two examinations subsequently. The urine showed a trace of albumin, many casts, which later increased in number; red cells also appeared later. Hemoglobin, 90 per cent. There was marked cyanosis, and the dyspnœa, with air hunger, was so severe that he could hardly rest at all at night. There was marked pulsation of the cervical vessels. There was enlargement of the liver and œdema of the lower extremities, which later increased. The extent of the tuberculosis in the chest was difficult to determine, but apparently this was a moderately advanced case.

Heart. There was a distinct heaving impulse in the fifth and sixth left interspaces, reaching in the latter situation nearly to the anterior axillary line. There was no thrill, but an uncertain presystolic impulse. The heart extended upward to the upper border of the third rib; on the right, a finger's breadth beyond the right border of the sternum; and to the left, nearly to the anterior axillary line. A systolic murmur was audible in the fifth and sixth left interspaces, from the sternum into the axilla, being most marked in the sixth interspace beyond the midclavicular line, in which location it was quite loud. It entirely disappeared before death. The first sound at the apex was weak and muffled and of very poor muscular quality. For a time it was almost entirely replaced by the murmur. Sometimes a long presystolic rumble was audible at the apex. The pulmonic second and aortic second sounds were never accentuated. Posteriorly, a systolic murmur was heard below the left scapula. The cardiac rhythm was usually fairly well preserved; at least, the individual cardiac cycles did not show much variation. The patient died at the end of seventeen days. The diagnosis of the heart lesion was probable endocarditis of the mitral

valve, mitral regurgitation, cardiac hypertrophy, myocarditis, and failing compensation. It was impossible, however, to exclude as the cause of the regurgitant murmur myocarditis in a heart hypertrophied in consequence of an antecedent nephritis.

SUMMARY. Murmurs over the chest not demonstrably dependent on cardiac or vascular disease, when listened for carefully, under favorable circumstances and repeated examinations, are found frequently in tuberculosis. They were heard in nearly three-fourths of our advanced cases. These murmurs are usually systolic in time and faint in intensity, in our cases three-fourths being faint. They are generally soft and whiff-like in character, though they may be quite loud and harsh. In the majority of cases these murmurs are heard repeatedly, and usually intermit only temporarily. The areas where they are most commonly heard, and where their maximum intensity most often occurs, are at the base of the heart, chiefly to the left of the median line, at the cardiac apex (a little over half as often as at the base), and at the inferior scapular angles posteriorly, more often on the left side. These murmurs are more frequent over the front of the chest than the back; they are more frequent and more widely distributed over the left side in front than the right. They are heard in a relatively small number of cases in the axillæ. They may be very limited in extent or may cover nearly the entire chest. In our cases the murmurs were usually heard best during the quietest part of the respiratory act, that is, during expiration or the respiratory pause, and during suspended respiration; less often they were limited to the end of inspiration and beginning of expiration, and rarely they were heard during inspiration only. These murmurs are modified at times by position, more often by excitement and exertion. With the possible exception of the left side in front, murmurs in advanced cases are heard more frequently over normal or hyperfunctionating tissue than diseased tissue, this being particularly noticeable at the bases posteriorly. The etiology of these murmurs is usually obscure, and causes probably responsible in a certain proportion of all cases are hard to establish in individual cases. In about 7 per cent. of our cases with murmurs, mitral regurgitation dependent on weakness of the heart muscle was diagnosticated. For prognosis and treatment, little is gained from these murmurs of undetermined origin. Even when they seem to depend on the advance of the tuberculous process they furnish little information unobtainable in other ways.

The diagnosis between cases with murmurs due to gross cardiac disease and those without any such cause demonstrable may be rendered very difficult in the presence of pulmonary tuberculosis, especially if it is far advanced. Tuberculosis has many symptoms found in heart disease, and often renders the physical signs of the heart inconclusive, in particular making the size of the heart difficult

to determine. The apical murmurs, in our experience, most frequently occasion uncertainty in diagnosis.

Out of 171 cases of pulmonary tuberculosis (over one-half being far advanced cases, and nearly three-fourths being females), a diagnosis of endocarditis was made in 2 cases (mitral regurgitation once, and mitral regurgitation and stenosis once), and a diagnosis of probable endocarditis (mitral regurgitation) was made in a third case. That is, endocarditis was diagnosticated in 2 or 3 of 171 cases. In none of these cases was a diagnosis of disease of the pericardium or of the aorta made. Myocarditis is not infrequently demonstrated microscopically in hearts from persons dying of tuberculosis, and its occurrence is often suggested clinically. The diagnosis, however, in individual cases of tuberculosis is usually very difficult, first, because of the frequent absence of important signs, for instance, certain types of arrhythmia; and, second, because many of the symptoms of myocarditis may also be produced by tuberculosis. Heart disease with failing compensation I have never met in very far advanced tuberculosis.

TWO CASES OF SOLITARY FALSE NEUROMA—PROBABLY NON-MALIGNANT.

By Edward M. Foote, M.D.,

ADJUNCT PROFESSOR OF SURGERY IN THE NEW YORK POLYCLINIC; VISITING SURGEON TO THE NEW YORK CITY HOSPITAL; ASSISTANT SURGEON TO THE NEW YORK SKIN AND CANCER HOSPITAL

From time to time there are reported cases of solitary tumors developing in nerves. Most of them are of small size and are composed of fibrous tissue. Sometimes the nerve fibers are easily separated from the tumor. At other times they form an integral part of its substance or are lost in the tissue of which the tumor is composed.

Within a year it has been my fortune to operate upon two patients suffering from a serious form of fibrous tumor affecting the nerves. As such condition is not adequately described in any one of a dozen well-known text-books on surgery and pathology which I have consulted, the details of these two cases seem worth recording.

Case I.—The first patient, M. S., came to me from Dr. Tukey, of Bridgeport, and Dr. Dougal Bissell, of New York. He was a young man, aged seventeen years, with an excellent family and personal history. Two years previous to my first examination he fell on the sidewalk while running, and struck his head so that he was unconscious for nine hours. His right shoulder and left leg were badly

bruised. In two weeks all symptoms had disappeared. Fourteen months after this accident there was noticed a swelling of the back of the left leg. This increased for about a year, and, according to his parents, it remained stationary afterward. There was absolutely no pain nor any disability. He had grown rapidly—gaining twenty-five pounds in six months.

Physical examination of the patient, made February 7, 1909, showed him to be an unusually well-developed young man, five

FIG. 1.—Fibrosarcoma of the deep fascia of the thigh and leg involving the sciatic nerve and some of its branches.

feet and ten inches in height, weighing one hundred and sixty-seven pounds. The lower half of the left thigh and the left knee measured from three to four inches more in circumference than the corresponding parts of the right limb. This difference was due to a hard, elongated swelling situated in the back of the thigh and leg. It was not attached to the overlying skin, but closely attached to the deep fascia. Its lower portion presented a distinct rounded outline; but the upper margin was lost beneath the deep muscles on the back of the thigh (Fig. 1). The whole tumor measured about sixteen

inches in length and five inches in width. It was so narrow in the fold back of the knee that it was difficult to say whether or not the portions in the calf and thigh were connected. Pressure upon the tumor produced no unpleasant sensation. There was a slight venous enlargement in the overlying skin, but there was no enlargement of the inguinal or other lymphatic glands.

A diagnosis of fibroma or an encapsulated sarcoma was made, and an immediate removal of the tumor (or tumors) was advised.

Operation was performed February 21, 1909, with the assistance of Drs. Bissell and Tukey. An incision was made directly down-

FIG. 2.—Portion of the tumor situated in the calf, after its removal. In the groove shown at the left of the picture lay the external branch of the popliteal nerve. At this level the internal branch of the popliteal nerve was wholly in front of the tumor.

ward from the popliteal space for a distance of six inches. Numerous enlarged veins were divided and ligated. The tumor was covered by deep fascia, to which it was not adherent. It was intimately attached to the fascia covering the gastrocnemius muscle. The external branch of the popliteal nerve was partially surrounded by the tumor, but was not attached to it. Finally, the whole of the tumor below the fold of the knee was cut from its deep attachments. Part of the aponeurosis of the gastrocnemius muscle had to be removed with the tumor. The latter was continuous with the mass in the thigh by an isthmus one and one-half inches wide and one inch thick. This was cut square across, and the lower portion of the tumor was removed. The wound was closed by suture and healed primarily.

The portion of the tumor removed measured four and one-half by five and one-half inches, and weighed nineteen ounces (Fig. 2). It was entirely composed of dense white fibrous tissue. It cut like sole leather. Dr. F. M. Jefferies, who made the pathological examination, reported it to be a fibrosarcoma (Fig. 3).

Three weeks later, assisted by Drs. Tukey and Roberts, of Bridgeport, I made an attempt to remove the remaining portion of the tumor in the thigh. The whole posterior surface of the tumor was exposed and the upper and lower portions of it were removed, as well as portions to the right and left of the sciatic nerve, but the main trunk of this nerve lay in the centre of the tumor and was so intimately connected with it as to be indistinguishable from the tumor itself.

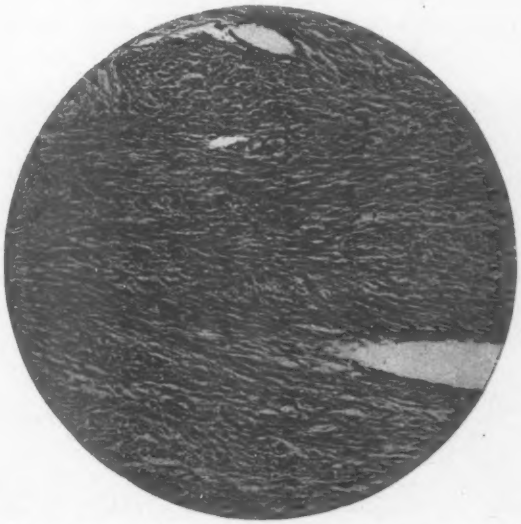


FIG. 3.—Tumor of the thigh involving the sciatic nerve (× 200).

The complete removal of the tumor, therefore, would have meant the sacrifice of the sciatic nerve. To this the parents would not consent. The wound was sutured and healed without difficulty. There was no paralysis of the muscles of the leg or foot. The only nerve injury at the operation was the cutting of a few small branches of the sciatic in the thigh.

November 21, 1909, the patient wrote me that the upper and lower part of his left leg measured the same as the right; that the centre of the thigh, where a portion of the tumor was left, was one inch larger in circumference than the right; and that there was no pain or discomfort in the leg. He said it felt just the same as the right

one, and that he never knew that he ever had trouble with it. He walks from three to five miles a day to and from school, dances, runs, and enjoys the best of health, never favoring himself in any way. He weighs one hundred and ninety pounds, a gain of twenty-three pounds since the operation. The flesh is hard and the muscle is the same in both legs. On April 13, 1910, his health was still perfect.

CASE II.—J. L. McM., a man, aged thirty-eight years, well developed and of previous good health, noticed twenty years ago a small swelling on the top of the right shoulder. There was no history of injury. This swelling remained small for eleven years, and then gradually grew until it was prominent above and below the right clavicle and well backward toward the cervical spine. It was painless until six months previous to his entrance to the New York Skin and Cancer Hospital, July 28, 1909. Since that time it caused him so much pain in the arm and shoulder that he finally had to give up work.

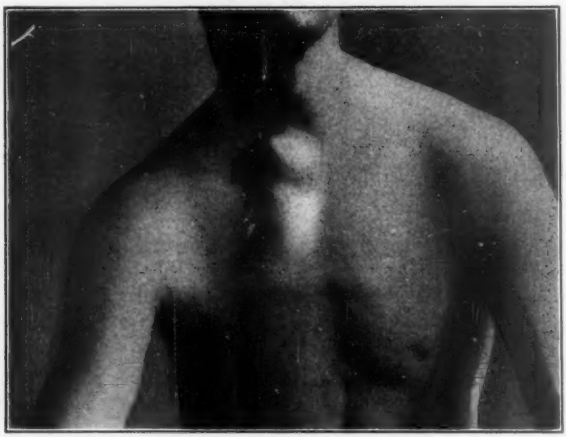


FIG. 4.—Fibroma of the brachial plexus, right side.

Physical examination showed a hard, immovable, rather nodular mass, close to the right side of the sternum, but extending nearly to the coracoid process and backward along the base of the neck nearly to the spine. The most prominent part of the mass was about the sternal articulation of the clavicle. It was covered by normal movable skin (Fig. 4).

Operation, July 29, 1909. An incision was made from the upper end of the sternum outward a distance of five inches and the tumor exposed. It was found to lie between the pectoral muscles and the ribs. It was intimately attached to both these structures, so that in dissecting it from the greater pectoral muscle it was necessary to

sacrifice a part of the latter; and to remove the tumor from the bones to which it was attached it was necessary to take away some of the periosteum. In spite of this intimate attachment it did not infiltrate the surrounding tissues after the manner of the usual forms of sarcoma, and the edges of the tumor were rounded and fairly distinct. Large portions of the tumor were dissected free and cut away until the cords composing the brachial plexus were exposed. The tumor was composed of dense, white fibers, which cut like sole leather. Toward the axillary margin of the tumor it was possible to distinguish it from the nerves which come from the brachial plexus. Toward the centre of the tumor the nerve trunks were apparently fused in the tumor in such a manner that they were indistinguishable.

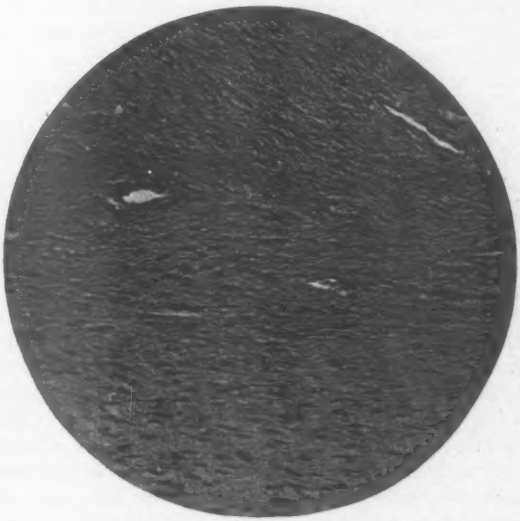


FIG. 5.—Tumor of the neck involving the roots of the brachial plexus (× 200).

To have removed the whole of the tumor would apparently have meant removal of the brachial plexus. A considerable portion of the tumor—probably more than half of it—was therefore left in position and the wound was closed. The patient was at once relieved of his pain. Tests of the motions of the arm made on the following day showed that there was no paralysis. The wound healed primarily. The sutures were removed August 5.

Pathological examination was made by Dr. H. H. Janeway, who pronounced the tumor a fibroma durum (Fig. 5).

November 15, 1909. Examination of the patient showed that there was little apparent increase in the size of the portion of the tumor

remaining, but the patient stated that for some weeks he had noticed pains in his arm at intervals and that their frequency and severity was on the increase.

December 2. Portions of the tumor were removed from above the clavicle through two incisions, one in the front and one in the back of the neck. In both instances the portions of the tumor removed were apparently connected with the deep cervical nerves, although the fibers could not be traced through the tumor. They seemed to lose themselves in its substance. The portion of the tumor removed from the back of the neck was closely adherent to the upper angle of the scapula. The patient made a good recovery from his operation, still retaining the various motions of his arm. He was for a time entirely free from pain.

January 24, 1910. He complained of pain between the upper angle of the right scapula and the median line. The arm was weak, though all motions could be made.

February 10, 1910. Pain was less severe, and the patient had gained seven pounds in weight.

March 25, 1910. He reported that his general health was good, that the arm was still weak, and that for a few nights he had a severe pain from the shoulder to the end of his fingers, lasting only a limited time.

These tumors offer so much that is interesting, that Dr. Janeway kindly made additional sections of both of them for comparison. He reported as follows: "I have cut sections from both tumors and believe them both to be fibromas. Sections from Case II gave no suggestions whatever of nerve tissue. The tumor is composed of abundant intercellular fibrous bands, in the meshes of which are branching connective tissue-cells of such a degree of development that it is impossible to consider them sarcomatous. The tumor from Case I has exactly the same structure, with the exception that the cells are even less sarcoma-like and the amount of intercellular fibrous tissue is greater. This tumor was very hard indeed, and it was very difficult to get thin sections from it. It is surely a mistake to consider either tumor sarcoma; and in this Dr. James Ewing, who also examined the tumors, agrees. It is true that local recurrence is possible, and in these cases almost certain, because of the impossibility of removing all the tumor tissue; but one need not fear metastasis unless the original tumor changes its character. In regard to the origin of these growths there are two possibilities. Either they originated from the connective tissue nerve sheaths, or the fascia external to the nerve sheaths and involved the nerves secondarily."

Since tumors of this character do not form metastasis, the outlook after complete removal is extremely good. Unfortunately, these two were so placed that their complete removal meant the loss of the use of a limb. I believe that the first patient should have

an amputation about six inches above the knee-joint. This would enable one to remove the tumor even though it extends as high as the sciatic foramen, and still leave a sufficient amount of material to cover the bone and form a serviceable stump. I so advised the patient, but his family would not consent to it.

In the second case complete removal of the tumor would necessitate amputation of the arm at the shoulder-joint, since it would probably be necessary to ligate and remove the axillary artery and vein as well as all the roots of the brachial plexus. I have hesitated to offer this advice until it is definitely shown that the palliative effects of the operation are only temporary.

I have been unable to find reported any cases exactly like these two. For the sake of comparison extracts from a few published cases are here mentioned, since they have some points of similarity with the two which are the subject of this sketch.

R. W. Smith[1] in his *Treatise on the Pathology, Diagnosis, and Treatment of Neuroma*, one of the most beautiful monographs that has ever been published, described the case of John McC., aged thirty-five years, who was admitted in 1840 to Richmond Hospital. He had a large tumor on the right side of his neck which existed for fifteen years without having caused the patient any pain. Three years later he was again taken to the hospital complaining of pain due to a large tumor in the back of the left thigh (Fig. 6). Subsequently, numerous small tumors developed in the peripheral nerves, and the patient died a few months later. Careful examination of all the nerves of the body showed that there were 1400 tumors growing in them, which were removed and counted. In the left sciatic and its branches there were more than 200. These tumors were recognized as being malignant, although at that time (1843), of course, no microscopic examination was made. The large tumor in the neck was associated with the right pneumogastric.

Herczel[2] reports a case somewhat similar to my second one, in which he removed by dissection a tumor involving the brachial plexus both above and below the clavicle. A new growth was disposed along some of the nerves of the plexus in a series of nodules more or less bead-like, and in places fused together. There was in no place any indication that the nerve fibers themselves had a part in the tumor formation. The tumor was a fibroma, showing in places myxomatous degeneration. It was combined with diffuse elephantiasis of the arm. The removal of this tumor produced paralysis of the biceps, brachialis anticus, and supinator longus muscles, with some loss of power in the flexors of the fingers. The tumor recurred after removal, especially in the forearm. In the skin of the upper arm there had been from birth an elevated, pig-

[1] A Treatise on Pathology, Diagnosis, and Treatment of Neuroma, Dublin, 1849.
[2] Beit. z. path. Anat. u. z. allg. Path., 1890, iii, 38.

mented area. This also increased in size. At the last observation, made nearly two years after operation, the paralyzed muscles had markedly atrophied. Otherwise the condition was about the same.

Hume[3] removed from a man, aged twenty-four years, six inches of the sciatic nerve with a tumor which involved it and extended from the gluteal fold to the popliteal space. In a month the patient was able to walk without support. All the muscles below the knee

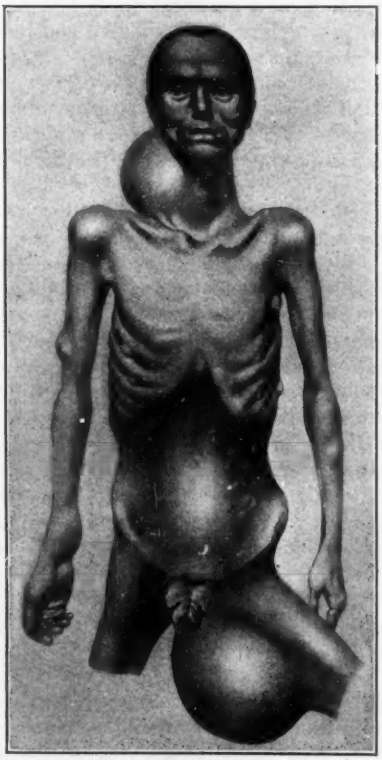


FIG. 6.—Multiple neuromas (case of R. W. Smith).

were paralyzed, and the patient used his leg like a flail, swinging it forward by means of the extensors of the knee. In another case he removed a tumor of the sciatic nerve from beneath the gluteus maximus of a man aged thirty-seven years. In this case it was possible to stretch the nerve sufficiently to effect a partial suture of the portions left by the resection of the nerve and tumor. Six months

[3] Lancet, 1891, ii, 654.

later he walked very well, being able to flex the leg on the thigh, but not to move the foot on the leg. The tumor in each case was a sarcoma.

Buchanan[4] mentions a case of tumor of the internal popliteal nerve. The tumor was about five inches long and completely filled the popliteal space. There was no paralysis or œdema of the leg. Amputation was performed through the thigh. The upper limit of this tumor was just below the division of the sciatic into internal and external branches. The sheath of the internal branch was stretched over the tumor and formed its capsule. On section strands of nerve fibers could be seen passing through the tumor growth. The tumor was soft and grayish in color, very vascular, and showing in places yellowish degenerative spots. The external popliteal nerve lay above the surface of the tumor, and was not involved in it.

Our knowledge of tumors of the peripheral nerves may be said to have begun in the year 1811, when Odier[5] suggested the name neuroma for "larger, movable, circumscribed, and deeply placed tumors, which are characterized by painful swelling of the nerves involved." It was not, however, until 1829 that an Edinburgh physician, named Wood,[6] accurately described the gross anatomy and symptoms of these tumors. He recognized the fact that they are composed chiefly of the connective tissue which surrounded the nerve fibers and not of the nerve fibers themselves.

Virchow[7] made an attempt to classify the various tumors connected with nerves, which up to that time were all included under the name neuroma. He distinguished between true neuroma, a tumor made up of new-formed nerve fibers, and false neuroma developing from the sheath of a nerve. He classed among the true neuromas the bulbous swellings often seen in the ends of the nerves of an amputation stump; but at the present time pathologists do not count these as tumors at all, since the various twisted nerve fibers which they contain are only a continued growth of the normal nerve fibers which have been cut across at the time of amputation. The division suggested by Virchow has been amplified by later investigators. For the sake of those who wish a complete classification, the following table is reproduced from Bruns'[8] book on *Tumors of the Nervous System*.

[4] Brit. Med. Jour., 1900, i, 955.
[5] Manuel de la médecine pratique, Genève, 1811.
[6] Observations on Neuroma, Edinburgh Med.-Chir. Transactions, 1829, iii, 367.
[7] Die Krankhaften Geschwülste, Berlin, 1863.
[8] Die Geschwülste des Nerven-Systems, Berlin, 1908.

- Neuromas
  - True
    - Neuromas containing ganglion cells.
      - The occurrence of true neuromas without ganglion cells is doubtful.
  - False
    - 1. Circumscribed or solitary tumors which spring from connective tissue of the nerve trunks or from that of the ganglia in connection with nerves.
      - Benign (Fibromas, myxomas, cysts, etc.).
      - Malignant (The various forms of sarcoma, also fibrosarcomas, myosarcomas, and cystic degenerated sarcomas.
    - 2. Diffuse overgrowth or multiple nodules of the connective tissue of nerves and their ganglia. Neurofibromatosis.
      - (*a*) Circumscribed or diffused and generalized fibromatosis of the nerve trunks.
      - (*b*) Plexiform neurofibromatosis.
      - (*c*) Neurofibromatosis of the skin (molluscum fibrosum).
      - (*d*) Elephantiasis neuromatosis.
      - (*e*) Malignant changes taking place in the tumors grouped under *a*, *b*, *c*, or *d*.
    - 3. Dejerine's interstitial hypertrophic and progressive neuritis of infancy.
    - 4. Thickenings of the nerves occurring in tuberculosis, leprosy, and syphylis.

I believe that the tumors which form the basis of this article belong in the benign or possibly the malignant group under division 1 of the false neuromas. The question may properly be raised whether they are nerve tumors at all. The fact that the edges of both tumors were found growing in fascia clearly outside of the nerve sheaths is the one point against such classification. But toward the centre in each case the relation of tumor to nerves was as intimate as it could possibly be. For purposes of both diagnosis and treatment, and for prognosis too, they are certainly tumors of the great nerve trunks. Whether they are such etiologically cannot perhaps be definitely proved unless an opportunity is had to dissect their deeper older parts.

These solitary peripheral neuromas may occur at any age; but according to Courvoisier[9] they are usually preceded by some traumatism. In the days of bloodletting the wound caused by this was often the starting point. The median nerve is oftenest affected; then the ulna, the sciatic, and the radial. The predominance in the upper extremity may be due to the more frequent traumatism of the hand and arm. The large majority of tumors do not exceed an inch in diameter. The very large ones are usually malignant. One diagnostic point for all neuromas is the fact that the tumor is movable from side to side and not in the direction in which the nerve runs. The benign tumors grow very slowly, often requiring decades to reach any considerable size. The malignant tumors may or may not grow rapidly. They show their malignancy by breaking through the outside sheath of the nerve and growing into the surrounding tissues, especially into the muscles. They may also spread farther into other tissues and set up metastasis in the same manner as malignant tumors starting in other structures of the body.

In strictly benign cases the nerve fibers often escape injury, so

[9] Die Neurome: Ein klinische Monographie, Basel, 1886.

that no symptoms are produced. This may also happen with malignant growths, but in that case there is likely to be at least pain. The pain may be very intense, and usually comes on in attacks. It is described as boring, sticking, burning, or like an electric shock. Changes in position, variations in temperature, and other slight causes may bring on these attacks. Sometimes by pressure the tumor causes pain in an adjacent healthy nerve. Other nervous manifestations are paresthesia, symptoms of motor irritation, anesthesia, and very rarely motor paralysis. Kölliker[10] says disturbances in sensation are more common than disturbances in motor power. Trophic disturbances rarely occur.

The diagnosis in multiple cases is usually easily made; in cases with a single tumor it is more difficult, unless the pressure of the tumor has given rise to some paresis, or unless direct pressure upon it produces symptoms of irritation in some nerve trunk.

If one has decided that a neuroma exists involving certain nerves, it is important to know whether the tumor grows from (*a*) the sheath of the nerve, the epinurium, or (*b*) the perinurium, which surrounds the smaller bundles of nerves, or (*c*) the endonurium, which surrounds the nerve fibers. In the first case the tumor may lie wholly outside of the nerve. Its removal under such circumstances is, of course, much easier, and may be accomplished without severing the nerve; but unfortunately this can only be decided by an operation.

A differential diagnosis between benign and malignant tumors can often be made. Slow growth is indicative of a benign tumor. Rapid growth, or rapidity of growth after traumatism, in the case of a long-standing tumor, suggests malignancy. Severe nervous attacks, anesthesia, and paralysis suggest malignancy. Other signs of malignancy are recurrence after operation in the same or in other nerves, infiltration of the surrounding tissues rendering the tumor immovable, involvement of the lymph glands or metastasis elsewhere, and ulceration of the overlying skin.

The prognosis in benign cases is good, but if it is necessary to cut the nerve to remove the tumor, even though it be sutured afterward, a guarded prognosis must be given. In the malignant cases prognosis is bad, but even in such cases a long time may elapse before a fatal termination is reached. Bruns mentions a recurrent neuroma in the sciatic five years after the removal of a similar tumor from one of the nerves of the foot. The tumor of the sciatic was removed, and the patient was free from recurrence fifteen years afterward. Other similar instances might be mentioned. In non-malignant cases prognosis is bad if there are multiple painful tumors. A patient so afflicted becomes cachectic, whereas in cases without pain he may live for many years.

When the diagnosis has been established it is by no means easy

[10] Deut. Chirurgie, 1891, Lief, 243.

to decide upon the form of treatment to be adopted. If the tumor is situated upon a small nerve leading to the skin the question of paralysis need not be considered; whereas, if it is upon an important nerve trunk the possibility of permanent injury of the nerve must be borne in mind, even in strictly benign cases. If the pain is intense, it may be better to run the risk of paralysis, or even deliberately to produce a paralysis, rather than to allow the patient to suffer repeated painful attacks. Indications for operation in malignant tumors are, of course, much stronger. The decision then will turn chiefly upon the possibility of a complete removal of the tumor.

The four forms which operation may assume are: (1) Extirpation of the tumor without division of the nerve; (2) extirpation of the tumor with resection of the nerve; (3) amputation of the limb; (4) neurotomy or stretching of the nerve involved. The choice of operation will depend in part upon whether the tumor is malignant or not and in part upon its relation to the nerve trunk. Hence the first thing to do is fully to expose the tumor; then, unless it is evidently of a malignant character, its relation to the nerve fibers should be ascertained, either by splitting its capsule or by splitting the tumor itself. If the tumor is so fortunately situated as to leave intact the whole or a large portion of the nerve, it can be removed without permanent injury. In the case of malignant tumors the same rule should be followed here as elsewhere and the incision made wide of the growth. The question of amputation of the limb will depend partly upon the nerve or nerves involved and partly upon the existence of metastasis. If a radical operation is impossible, but pain is intense, it may be possible to divide the affected nerve on the proximal side of the tumor.

If the tumor is a benign one, and yet its removal necessitates resection of the nerve, it may be possible to restore the continuity of the nerve by suture. Hume attempted this in one of his cases, and succeeded in obtaining voluntary control of part of the muscles supplied by the divided sciatic. Possibility of restoration of sensation after suture of the nerve is, of course, greater than restoration of motion. This is especially true after suture of the median and other nerves of the arm. The anastomosis of fibers of the different nerves permits a partial restoration of function, which makes it very difficult to estimate the effect of a nerve suture in the arm. Primary restoration of nerve function after suture in the sense of primary union of a wound is absolutely unknown. Courvoisier called attention to the fact that recurrence after extirpation does not often take place, even in cases in which amputation has been performed for malignant tumors of nerves. One evil effect of operation which was formerly rather common was tetanus; with the cleaner surgery of today this need not be feared.

REVIEWS.

A Handbook of Medical Diagnosis. By J. C. Wilson, A.M., M.D., Professor of the Practice of Medicine and Clinical Medicine in the Jefferson Medical College, Philadelphia. Pp. 1435; 422 illustrations. Philadelphia and London: J. B. Lippincott Company, 1909.

Professor Wilson's *Handbook of Medical Diagnosis* is an ambitious volume: it is large in size, larger than any other in the English language, and comprehensive in scope. It is divided into four parts, of which the first treats of medical diagnosis in general, medical topography, the examination of the patient, and case-taking; the second, of the methods of diagnosis and their immediate results, including physical diagnosis, laboratory diagnosis, as well as examination of the eye, and the use of the *x*-rays; the third, of the symptoms and signs of disease; and the fourth, of the clinical applications of what has preceded in the diagnosis of the many different diseases. As a matter of fact the first three sections of the book (about 600 pages) comprise what would ordinarily be included in a handbook of diagnosis or of methods of diagnosis, while the last section (about 800 pages) is devoted to a discussion of subjects ordinarily included in a practice of medicine—definition, etiology, morbid anatomy, symptoms, diagnosis, and prognosis: treatment only is wanting.

Of the first part, one must say that it has been well done. The introductory remarks on diagnosis—direct and indirect—are extremely pertinent, and really should be read. The chapter on medical topography comprises a brief and satisfactory discussion of the topographical relations of the various landmarks of the body and the viscera, of value in all diagnostic procedures; and the chapter on case-taking includes all that is necessary to the subject. Of the subjects discussed in the second part, most interest undoubtedly attaches to physical diagnosis—inspection, palpation, mensuration percussion, and ausculatation—to which 133 pages are devoted. This in general is a reflection of recognized facts and opinions, tinctured by the author's wide experience and ripe judgment. There is much that is excellent; for instance, the distinction drawn between loudness and accentuation of the heart sounds: loudness is said to be a matter of degree, accentuation a matter of quality, conveying the idea of suddenness, sharpness, and a certain vibrating

quality due to quick and sharp tension. Some of us, however, hardly dissociate entirely the element of loudness from accentuated heart sounds, as Dr. Wilson seems to imply. The apex of the heart is correctly said to be 2 to 3 cm. below and to the left of the maximum beat. It would have added to the interest of the discussion to have included an interpretation of sphygmograms in the light of our newer knowledge of cardiac physiology and pathology. Although it is true that a thrill at the base of the heart of maximum intensity in the aortic area is common in aortic stenosis, this thrill is systolic in time (which is not mentioned on page 94), and a systolic thrill in the same region occurs commonly in the absence of stenosis of the aortic orifice. Some confusion is likely to arise from the use, in regard to percussion, of the term "clear" for what is perhaps the more commonly employed term "resonant," and from a description of normal tympanitic areas in the chest; at the most these areas yield a note of mixed pulmonary resonance and tympany. "Subcrepitant" applied to a rale is a really bad term and, although rather widely employed, should be discarded. The discussion of the methods of examining the stomach, intestines, upper air passages, blood, urine, sputum, transudates, exudates, the nervous system, and the eye are admirable. Attention might be directed to the absence of mention ofthe benzidine test for occult blood; and it would not have been amiss to have included some discussion of the methods of estimating the functional capacity of the heart, kidneys, etc. The diagnostic uses of the *x*-rays are well portrayed.

Part III, devoted to the symptoms and signs of disease, includes a discussion of the general appearance of the patient, temperament, and diathesis; the facies, weight, form and nutrition; the bones, joints, musculature, posture, attitude, and gait; the heat mechanism and fever; respiration, cough, and expectoration; the different types of pulsations; and the various manifestations of disease of the different systems of organs. Amidst a plethora of excellent matter it is difficult to pick out any one topic for special mention, but attention may well be drawn to the excellent discussion and analysis of pain. Part IV, is, as has been said, a modified practice of medicine—minus treatment. In general this is all that reasonably could be desired. The portrayal of the clinical aspects of disease and of their differentiation is clear and to the point; there are few omissions and still fewer misstatements. Mention should have been made of searching the urine for lead in cases of lead poisoning. Gallstones are still believed to rest quiescent in the gall-bladder in many cases without causing symptoms, although it has been well demonstrated that they frequently provoke divers sorts of "indigestion." On the contrary, Dr. Wilson well points out the fact that symptoms of gallstone colic are sometimes present in acute cholecystitis without gallstones; this is only part of the evidence that most cases of gallstone colic are really attacks of acute cholecystitis. The bad classification of chronic

interstitial hepatitis, or cirrhosis of the liver, depending upon the size of the liver, that is, upon whether it is of about normal size, atrophic, or hypertrophic, is adhered to, although as a matter of fact the size of the liver bears no constant or direct relation to the other phenomena of the disease. It is somewhat of a shock to be told that the right-sided hydrothorax of cardiac disease is probably due to the larger space in the left thorax occupied by the enlarged heart. The symptomatology and diagnosis of diseases of the blood and the ductless glands are very well described; but the characteristic remissions of pernicious anemia might have been more emphasized. There is no mention of the unusual cases of chronic adhesive pericarditis that run their course under the guise of cirrhosis of the liver with ascites; nor of Traube's sign in aortic insufficiency, nor is an explanation of the cause of the Flint murmur attempted. The murmur of mitral stenosis is correctly said to occupy the entire diastolic period in the greater number of cases. Much more might be said—mostly in praise of the volume.

Dr. Wilson set himself the task of encompassing within a single volume a description of clinical phenomena, and of correlating with these, complexes of clinical phenomena that constitute diseases, in such a manner that the practitioner who seeks information upon an obscure case may at once turn to the discussion of the methods available to clear it up, and the student may find the definite clinical applications of the same methods and their results in descriptive medicine. How well he has accomplished his task must be immediately apparent to any one who reads the book. If some of the foregoing remarks be construed as adverse criticism, one must hasten to add that they are minimal as contrasted with the general excellence; they are scarcely blemishes on a masterpiece. The book throughout reflects thoroughness and care in preparation; it is well arranged, lucidly written, and admirably illustrated; it is a credit to its author, and assuredly will meet, as it merits, a cordial reception on the part of the profession. A. K.

THIRD REPORT OF THE WELCOME RESEARCH LABORATORIES AT THE GORDON MEMORIAL COLLEGE, KARTOUM. By ANDREW BALFOUR, M.D., Director. Pp. 477; 266 illustrations. London: Baillière, Tindall & Cox, 1909.

THE director of the Wellcome Research Laboratories in Khartoum aims to issue a report at intervals of about every two years. This recently published third report leaves no doubt of the breadth and usefulness of the work which the laboratory has carried on. The subjects are so multiple that the book contains discussions in many of the biological sciences as they apply to the Sudan. The director

contributes a number of papers dealing with the protozoan diseases in man and in various domestic animals, and trypanosomiasis, hemogregarine, and spirochetosis of fowls are discussed. The subject of kala-azar as found in the upper Nile region is interestingly considered by other authors, special reference being made to the sanitary problems involved. The zoölogical papers concern, among other subjects, the reptiles and poisonous snakes of the Anglo-Egyptian Sudan. An extensive report by the economic entomologist is published, while several papers deal with characteristics of negroid tribes, ethnological specimens, and native medical practice in an interesting manner. The report of the chemical section deals largely with a research upon the native vegetable germs. The report contains and aims to disseminate much information of practical value to the people living in British African possessions, although many facts of purely scientific interest are also set forth. A noteworthy feature of the book is the illustration, consisting of colored plates, microphotographs, charts, maps, and photographs. The report reflects much credit on the director and the band of workers about him, who are making such strides toward bringing the Sudan into a higher state of civilization, and who are doing so much to elucidate the many problems in the natural sciences which abound in that country. G. C. R.

PROGRESSIVE MEDICINE. A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES, AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART ARMORY HARE, M.D., Professor of Therapeutics and Materia Medica in the Jefferson Medical College; Assisted by H. R. M. LANDIS, M.D., Demonstrator of Clinical Medicine in the Jefferson Medical College, Philadelphia. Vol. I, March, 1910; pp. 322; 8 illustrations. Philadelphia and New York: Lea and Febiger, 1910.

THE first volume of *Progressive Medicine* for 1910 opens with an instructive chapter of almost one hundred pages on the surgery of the head, neck, and thorax, by Charles H. Frazier. Special attention is devoted to trigeminal neuralgia, facial paralysis, brain tumors (including those of the hypophysis), papillœdema, hydrocephalus, cranial trauma, rhinoplasty, carcinoma of the lip, tongue, tonsils, and larynx, tuberculosis of the cervical lymph nodes, aberrant thyroids, goitre, tuberculosis and tumors of the mammary gland, empyema, pneumectomy with the aid of differential air pressure, the surgical treatment of pulmonary tuberculosis, wounds of the lung and of the heart, œsophagoscopy, and other important subjects. John Ruhräh has a chapter of eighty pages on the infectious diseases, in which he discusses especially the principles of the Wassermann

and similar reactions, the transmission of infectious diseases, pathogenic protozoa found in man, the treatment of acute infectious diseases with extracts of washed leukocytes (Hiss), vaccine therapy, cerebrospinal fever, "common colds," dengue, diphtheria, the "fourth" and the "fifth" disease, glanders, kala-azar, leprosy, malaria, measles, pneumonia, anterior poliomyelitis, rabies, Rocky Mountain spotted fever, scarlet fever, sleeping sickness, tuberculosis, typhoid fever, uncinariasis, pertussis, etc. Floyd M. Crandall devotes thirty-two pages to recent progress in diseases of children, discussing particularly infantile mortality, the care of the newborn infant, asphyxia neonatorum, septic infection and icterus in the newborn, the urine in infancy, status lymphaticus, rachitis, functional neuroses in children, infant foods, breast feeding, and artificial feeding. D. Braden Kyle devotes fifty-four pages to rhinology and laryngology, in which he treats especially of "taking cold," the treatment of chronic disease of the nose, recurrent nasal hemorrhages, hay fever, nasal tuberculosis, scleroma of the upper respiratory tract, sarcoma of the nose, the relation of the optic nerve to the nasal sinuses, suppuration of the accessory sinuses, pharyngoscopy, the faucial tonsils and the teeth, tonsillectomy, cicatricial stenosis of the larynx, laryngeal tuberculosis, voice production, phonasthenia in singers, etc. Arthur B. Duel devotes thirty-six pages to otology, treating especially of the labyrinth and its disorders, suppurative otitis, sinus thrombosis, syphilis in relation to the ear, and deaf mutism. The volume, as preceding volumes, merits the careful attention of all who would keep abreast of the progress of present-day medicine. A. K.

MEDICAL GYNECOLOGY. By SAMUEL WYLLIS BANDLER, M.D., Adjunct Professor of Diseases of Women, in the New York Postgraduate Medical School and Hospital. Second edition; pp. 698; 150 illustrations. Philadelphia and London: W. B. Saunders Company, 1909.

THE publication of a second edition within the year speaks well for the value of this work. As stated in the review of the first edition, in these columns, the book is a most complete exposition of non-operative gynecology. The present edition is a little larger than the earlier one, a matter of some twenty pages, due to the incorporation of new material, particularly in relation to the so-called Head zones, an instance of unfortunate nomenclature, together with several other and less extensive additions. It gives us pleasure to reiterate at this time the opinion formed by the critical review of the first edition, namely that the work is most satisfactory and that it will be found to be a valuable addition to the library of the general practitioner. W. R. N.

A Textbook of Practical Therapeutics. By Hobart Amory Hare, M.D., B.Sc., Professor of Therapeutics and Materia Medica in the Jefferson Medical College, Philadelphia. Thirteenth edition; pp. 958; 126 illustrations. Philadelphia and New York: Lea & Febiger, 1909.

The publication of a thirteenth edition of a book is in itself sufficient evidence of its unusual merit; and when to this is added the fact that a second Chinese edition has been published and that a Korean edition is about to be issued, the ever-widening sphere of influence of the book is immediately apparent. In the latest edition, Dr. Hare has, as he has heretofore, thoroughly revised his *Therapeutics*, so as to have it fully abreast of the times and make it adequately meet the requirements of the general practitioner. Among the inclusions, one may mention, the use of atoxyl as a substitute for the older arsenical preparations, and especially its use in syphilis; phenolphthalein in constipation; salicylate of ethyl and novaspirin in rheumatic and gouty affections and aspirin locally in tonsillitis; magnesium sulphate locally for the relief of pain and inflammation; picric acid in burns; urotropin to prevent cholecystitis in typhoid fever and infection after injury of the cerebrospinal system; the Lenhartz method of treating gastric ulcer; Murphy's method of treating septic peritonitis; antitoxins for gonorrheal infections and cerebrospinal meningitis; and recent researches on anesthetics. The book thus comprises not only a discussion of materia medica, and of the properties and actions of drugs and other remedial measures, but also describes the practical applications of these measures to the every-day treatment of disease. There is perhaps no more popular book, and none more deservedly so. In its new edition it will unquestionably maintain the enviable position that it has achieved, and it must also command an ever increasing circle of professional adherents. A. K.

A Text-book of Obstetrics. By Barton Cooke Hirst, M.D., Professor of Obstetrics in the University of Pennsylvania. Sixth edition; pp. 992; 847 illustrations. Philadelphia and London: W. B. Saunders Company, 1909.

One of the developmentary changes in medical work, destined before long to become a matter of common acceptance by the profession and the public, and even now beginning to be appreciated, is that obstetrics is a branch of surgery. The ordinary obstetric case should have for its safe conduct a degree of asepsis not less than is demanded by other procedures recognized to be within the domain of surgery, while operative obstetrics is of course admittedly surgical.

The truth of the foregoing being self-evident, it naturally follows that a man competent to handle ordinary obstetric complications will be expected, and must without question be prepared, to treat the consequent lesions or the complications of the child-bearing process. In other words, the obstetrician of the present and future must be a skilled gynecologist. In his preface to this, the sixth edition of his work, the author emphasizes the essential connection between these two subjects, and calls attention to the futility of advising various needful operative procedures in obstetric text-books without advice as to the necessary technique of their performance. He has, therefore, in the present edition included in his section on operative obstetrics a full consideration not only of the so-called obstetric operations, in the usually accepted narrow meaning, but also those operative procedures commonly classed under the artificial limitations of gynecology.

The previous editions of this work have made its character and scope so well known that it seems unnecessary to review it again in these pages in extenso. The wide experience of the author as a teacher and operator has enabled him to produce a book which, in scope and detail, is not surpassed by any other yet published upon this subject. W. R. N.

ORGANIC AND FUNCTIONAL NERVOUS DISEASES. By M. ALLEN STARR, M.D., Ph.D., LL.D., Sc.D., Professor of Neurology in the College of Physicians and Surgeons, Columbia University, New York. Third edition; pp. 911; 329 illustrations. Philadelphia and New York: Lea & Febiger, 1909.

But two years have elapsed since the publication of the second edition of Dr. Starr's well known book of *Organic and Functional Nervous Diseases*, and a demand is made for a third: certain evidence of intrinsic worth and merit. The opportunity was embraced to revise, and rearrange the contents and to make many additions. The general aspects of neurology, including anatomical and physiological details, the method of examining a patient, the various symptoms presented by nervous affections, and the principles of diagnosis, have been brought together in the first part. The organic diseases are discussed in the second part; such additions as have been made to our knowledge of the nervous system since the publication of the second edition have been incorporated; and the chapters on beri-beri, caisson disease, and syphilis have been rewritten. The functional nervous diseases are discussed in the third part—which has been about doubled in size. In the fourth part the diseases of the sympathetic nervous system are discussed, our present knowledge of vasomotor affections, their physiology and pathology being sum-

marized, and chapters added on symmetrical gangrene, angioneurotic œdema, and the trophic symptoms occurring in nervous disorders. The indications for surgical intervention in many disorders of the nervous system and the operative procedures to be elected are fully set forth, all of which is based upon a large personal experience as well as judicial sifting of the writings and experience of others. The book assuredly is of much value and a credit to its author; it must continue to enjoy the favor of the profession. A. K.

THE INTERPRETATION OF RADIUM. By FREDERICK SODDY. M.A. of the University of Glasgow. Pp. 256; 31 illustrations. New York and London: Putnam, 1909.

THIS book aims at a presentation of the present-day views of radium, as an element undergoing spontaneous disintegration. Non-technical language is used, so that the ideas involved may be comprehended by the lay reader. Beginning with a description of radio-activity and its effects, the history of the discovery of radium and the development of our knowledge of its properties are considered in logical order to the latest view that lead is the end product of a series of changes which begins in the element uranium. Briefly, each of these changes consists of the giving off of an atom of helium from an atom of uranium or one of the resultants, each change reducing the element to the next lower in the series. Uranium has an atomic weight of 238, and lead 206, the difference between them representing eight atoms of helium given off at eight different periods of disintegration. This process constitutes a veritable transmutation of elements. The subject deals in measurements so enormously large and so infinitely small that it taxes the imagination of the reader to comprehend it. For instance, the "average life" of uranium is 7,500,000,000 years, and "a grain of radium bromide expels every second about ten thousand million particles throughout many centuries." One pound of uranium contains latent energy equal to that of 900 tons of coal, etc. The application of radium to medicine is not discussed, but the last chapter is devoted to speculation as to the results to the human race of future generations of the possible utilization of the enormous energy stored in matter. Taken as a whole, the work is clear and convincing, and the illustrations are of material aid to an undertsanding of the methods employed in investigating this subject. S. D. I.

PROGRESS

OF

MEDICAL SCIENCE.

MEDICINE.

UNDER THE CHARGE OF

WILLIAM OSLER, M.D.,

REGIUS PROFESSOR OF MEDICINE, OXFORD UNIVERSITY, ENGLAND,

AND

W. S. THAYER, M.D.,

PROFESSOR OF CLINICAL MEDICINE, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MARYLAND.

Blood Findings in Pulmonary Tuberculosis.—STEFFEN (*Deut. Arch. f. klin. Med.*, 1910, xcviii, 355) has made a careful examination of the blood of 79 tuberculous individuals (sanitarium patients). In all instances the blood was obtained between the hours of 6 and 7 A.M. Differential counts were made of specimens stained with Leishman's stain, 1000 cells being counted as a rule. The chief interest centres in Steffen's findings with regard to the lymphocytes and polymorphonuclear neutrophiles. In chronic afebrile cases the polymorphonuclear neutrophiles are normal (absolute number), and lymphocytes are about doubled in number. In acute defervescing cases, the polymorphonuclear neutrophiles are normal or slightly diminished, whereas lymphocytes are two to three times the normal number. In the severe (advanced) cases there is an increase of the polymorphonuclear neutrophiles. Cases of moderate severity show, as a rule, an absolute increase of both polymorphonuclear neutrophiles and lymphocytes. Steffen believes that the lymphocytosis is to be attributed to the tuberculous process *per se*. As soon as the infection becomes mixed, with ulceration and caseation, a polymorphonuclear neutrophile increase may be expected, its extent being governed by the same factors which are operative in any pyogenic process. The lymphocytosis which occurs early is of considerable diagnostic value. True, such a finding may occur in lues, Basedow's disease, whooping-cough, nephritis, etc., but the finding of an abnormally large number of lymphocytes should awaken one's suspicions, and in the presence of other signs it is confirmatory evidence. Lymphocytosis may occur before bacilli are demonstrable in the sputum. In an outspoken case of pulmonary tubercu-

losis, the author believes one may draw definite conclusions as to the nature of the pulmonary process—whether tuberculous alone or secondarily infected—from the differential count, and, in a general way, as to the predominance of one or the other factor.

Determination of Urinary Ammonia and Acidity.—Bjorn-Anderson and Fauritzen (*Hoppe-Seiler's Zeit. f. physiol. Chem.*, 1910, lxiv, 21) describe a simple and rapid method for determining urinary ammonia and acidity. Comparative tests show that the NH_3 values are constantly a little too high. The principle of the method is as follows: We have, let us say, one fluid which contains n equivalents of an acid—HCl, for example—and m equivalents of an ammonium salt, such as NH_4Cl. Since the latter is neutral in reaction, n alkali equivalents will be necessary to neutralize the fluid. If formalin (40 per cent. formaldehyde) be added to a fresh portion of the fluid, it unites with the NH_3 of the ammonium salt to form hexamethylentetramin, and hydrochloric acid is set free. On titrating now, it will require $n + m$ alkali equivalent to neutralize (n for the original acid present and m for the acid set free by the formalin). By subtracting the first value (cubic centimeter of N/10 alkali) from the second, one obtains the number of acid equivalents which were bound by NH_3. The quantity of ammonia in grams is obtained by multiplying by 17. Before titrating, the fluid should be saturated with neutral potassium oxalate, as Folin has shown, to remove the calcium. Method of titration: To 20 c.c. urine add 20 grams of finely powdered neutral potassium oxalate and 5 drops of 0.5 per cent. solution of phenolphthalein. Now add N/10 NaOH to neutralization. The number of cubic centimeters required is noted and then 5 c.c. formalin (neutralized, if necessary) is added. Again add decinormal alkali sufficient to neutralize. The quantity of alkali used in the last titration indicates the amount of acid which was bound by ammonia. The fact that the readings are somewhat high is probably due to the presence of amino-acids in the urine, since formaldehyde unites with the amino group and liberates the acid radicles. In following the urinary acidity and ammonia in diabetic acidosis during the last three years, it has been found that the method gives satisfactory results. It has been noted that the ammonia and acidity curves run a parallel course. This parallelism has been seen in health as well as in diabetics and, apparently, has not been previously observed. It shows that one can follow the variations in the degree of acidosis by determining the total acidity of the urine. In recent years there has been much discussion as to whether the absolute amount of NH_3 or the ratio of NH_3 nitrogen to total nitrogen is of greater value in determining the grade of acidosis. Bjorn-Anderson and Fauritzen believe that the absolute amount of NH_3 is the more important.

Experimental Acute Nephritis.—Pearce, Hill, and Eisenberg (*Jour. Exper. Med.*, 1910, xii, 197) have continued on dogs the experimental work done by Schlayer and his associates on rabbits. Their studies have been especially directed to the vascular reactions which are present in the tubular and vascular types of nephritis. Potassium chromate, uranium nitrate, and corrosive sublimate produce lesions

which are, in the early stages, of a nearly pure tubular type, while arsenic and cantharidin cause directly vascular disturbances. Late tubular nephritis is of a more mixed type. The vascular reactions of the kidney were determined by measuring with an oncometer the changes in the volume of the organ occurring under the influence of adrenalin to cause contraction of the vessels, and of caffeine and sodium chloride to test dilatation and diuresis. In the early cases of tubular nephritis the animals usually present an initial polyuria; the vascular reactions are normal or exaggerated, and with increased dilatation due to the administration of caffeine and salt solution, there occurs a correspondingly greater diuresis. While these cases show no anatomical lesions in the golmeruli, the exaggerated vascular reactions and increased diuresis point to a functional disturbance of the vessels, presumably an increased excitability. The vascular poisons, arsenic and cantharidin, on the other hand, produce little injury to the epithelium, but tend to cause anuria, and are characterized by minimal contraction and dilatation of the vessels, and little or no flow of urine. The late cases of tubular nephritis may be divided into two groups: One, the anuric form, is accompanied by severe gastro-intestinal disturbance and evidence of approaching anuria; physiological tests show diminished power of dilatation of the vessels, and corresponding inhibition of diuresis. The second form, the polyuric, is characterized by a condition of polyuria up to the moment of anesthesia. Physiological tests show that the power of dilatation is retained, but little or no diuresis occurs. The vascular incompetency in the late stages of the anuric form of tubular nephritis may be a natural consequence of the vessel irritability seen in the early stages, or it may be due to the elimination of secondary poisons through the glomeruli. The impermeability of the glomerulus following anesthetization in the polyuric form is as yet unexplained. Studies of the elimination of nitrogen were carried on in the same experiments. In tubular nephritis, especially the type produced by uranium, the output of nitrogen is diminished, and with its retention gastro-intestinal disturbances appear. There is, however, no appreciable change in the amount of nitrogen in the fæces, so that the intestinal symptoms do not depend on the elimination of toxic bodies of nitrogenous nature through the intestine. In the vascular nephritis caused by arsenic, the nitrogen elimination is increased owing to the increased metabolism caused by arsenic. It may be markedly diminished, however, by the administration of uranium nitrate. The general results obtained incline the authors to conclude that while it is not possible to demonstrate that an experimental nephritis may be purely tubular or purely vascular, lesions may be recognized which are predominantly of one type or the other, or which change rather sharply from one to the other type, and are, therefore, of great value in the study of problems of nephritis.

The Effect of Serum Injections on the Eosinophiles and Mastzellen in Man and Animals.—SCHLECHT (*Deut. Arch. f. klin. Med.*, 1910, xcviii, 308) reports interesting changes in the leukocytic formula following injections of antidiphtheritic and other sera. In diphtheria in man, when untreated with antitoxic serum, there is an initial leukocytosis of the polymorphonuclear neutrophile type, other cells showing no increase, eosinophiles and mastzellen often disappearing. While the

febrile reaction persists, the neutrophiles gradually diminish and there is a more or less marked reparatory increase of the large mononuclears. With defervescence there is a lymphocytosis, and coincidently the eosinophiles and mastzellen reappear and may even be more numerous than normally. When antidiphtheritic serum is given, the blood picture is altered. Within twenty-four hours after the first serum injection, an eosinophilia often appears and persists into convalescence. This amounted to 18 per cent. in one case (10,000 white blood corpuscles per 1 cm.); in another 14 per cent. of 13,000 leukocytes. Schlecht resorted to animal experiments to determine whether the eosinophilia resulted from the antitoxin, the serum, or the carbolic acid used as a preservative. Young guinea-pigs were used. Schlecht's observations on man and animals led to the following results: (1) Eosinophilia may be produced in man by the injection of antidiphtheritic serum; as a rule, children react more rapidly and oftener than adults. The reaction has no prognostic value. (2) Animal experiment shows that the reaction is not specific for antidiphtheritic serum, but that it may follow the injection of any foreign serum. (3) Usually there is an initial drop in the number of leukocytes with hypo-eosinophilia; an increase in the white count and hypereosinophilia quickly ensue. (4) In addition to eosinophilia, guinea-pigs show a great increase in the number of mastzellen following the injection of serum, the two appearing together or independently. (5) No increase of mastzellen occurs in man or the dog. The cause of the reactions is found in functional hyperactivity of the bone marrow.

SURGERY.

UNDER THE CHARGE OF

J. WILLIAM WHITE, M.D.,

JOHN RHEA BARTON PROFESSOR OF SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE UNIVERSITY HOSPITAL,

AND

T. TURNER THOMAS, M.D.,

ASSOCIATE IN SURGERY IN THE UNIVERSITY OF PENNSYLVANIA; SURGEON TO THE PHILADELPHIA GENERAL HOSPITAL, AND ASSISTANT SURGEON TO THE UNIVERSITY HOSPITAL.

Intravenous Narcosis.—KUETNER (*Zentralbl. f. Chir.*, 1910, xxxvii, 233), having employed this method of narcosis in one case unsuited for inhalation or local anesthesia, and being impressed by its success and apparent lack of danger, enlarged its use and now has employed it in 23 cases. He does not recommend it, however, but warns against it, In spite of all care and the exact observance of Burkhardt's precautions, thrombosis can occur at the site of the infusion even during the anesthesia. In two cases the saline infusion containing the ether failed to flow into the vein, and it was necessary to expose a second vein. During the operation on one case, the removal of a sarcoma in the gluteal region

involving the pelvis, the patient suddenly became cyanotic, the blood dark and the breathing shallow and rapid. The pulse, however, remained good and the pupils reacted. The infusion was stopped immediately, and the normal condition soon returned. Investigation showed that the vein was completely closed by a recent thrombus, the size of a pea. The transitory disturbance was probably due to an embolus. On the following day there was much disturbance in breathing, although the general condition was good. In another case in which there was no disturbance at the time of operation, on the day following operation, an extensive infiltration of the right lung was found and there was fever. The method, nevertheless, has advantages for the patient and the operator, especially in extensive operations about head and neck; and it is hoped that improvement in it may avoid its present dangers.

The Technique of Hemostasis in Operations on the Skull.—VORSCHUETZ (*Zentrbl. f. Chir.*, 1910, xxxvii, 274) provides hemostasis in the central flap by the use of a needle passed from one side to the other, under the base of the flap between the periosteum and bone, 1 cm. below the end of the flap. There is an outer band with a hinge at one end and a spring catch at the other, which encloses the end of the needle and provides compression of the bloodvessels entering the flap. When the flap is outlined by the incision, the peripheral edge of the incision is compressed by a series of hemostatic clamps with wide jaws, the handles of the clamps being directed away from the wound and lying in contact with the surrounding scalp out of the way. The advantages of the method are: the rapidity with which the edges are caught; retractors are unnecessary, since the clamps are used for this purpose; the clamps are so shaped and directed that they are not in the operator's way; the skin is not pulled out of place so that the topographical lines on the surrounding skin are not distorted. The skin sutures for closing the wound should be close together, about 0.5 to 1 cm. apart, and if a vessel spurts it should be enclosed in the suture.

Studies on the Infusion of Physiological Saline Solution.—THIES (*Mitt. a. d. Grenz. d. Med. u. Chir.*, 1910, xxi, 239) says that the physiological (9 per cent.) or the pure saline solution is not entirely suitable for infusion in the sick. They may, under certain circumstances, lead to severe disturbances and are to be avoided, especially, in small children, in patients who have lost much salt in conditions of hunger, in cachexia, and in patients who have associated pathological conditions of the kidneys, heart, and vascular system. It is not to be employed in those in whom there is a retention of sodium chloride, or an increased secretion of other salts, and is to be avoided in all fever patients. It is likewise to be excluded in cholemia, and should not be employed when large quantities of saline solution are required. The danger to the body is the greater, the greater the substitution of the alkaline substances of the cells for the sodium, which alters unfavorably the normal relations in the cell protoplasm. Since potassium and calcium are important metals for the preservation of life and function, it is necessary to prevent crowding them out of their relative positions by the presence of the sodium in the saline solution. Potassium and calcium should be added

to the sodium chloride in the solution, about in the proportion in which they occur in the body, that is, sodium chloride about 0.6 per cent., calcium chloride about 0.02 per cent., and potassium chloride about 0.02 per cent. This solution is hypotonic in relation to the serum, yet the injury which may result from this is less than that which would result from a pure sodium chloride solution. If the solution is to be isotonic to the serum, as is desirable in subcutaneous infusions, then not only the sodium chloride but the potassium and calcium salts also should be increased, so that the following proportions are present: sodium chloride 0.85 per cent., potassium chloride 0.03 per cent., and calcium chloride 0.03 per cent.

The Treatment of Hydrocephalus with Repeated Puncture.—KAUSCH (*Mitt. a. d. Grenz. d. Med. u. Chir.*, 1910, xxi, 300) says that in hydrocephalus in children, when the skull is wide open, the ventricular puncture should be made through the opening in the skull. The degree of pressure should be determined at the beginning and ending of the puncture. At the first puncture in severe cases, about 100 cm. should be withdrawn. The increased pressure should sink, about 20 cm. of water, but not lower than + 5 cm. If the child bears this well, at the next puncture the pressure should be brought down to 0, and later to minus. The quantity evacuated each time can be increased gradually to 200 or 300 cm. The puntcure should be repeated as soon as a higher positive pressure is suspected, if necessary daily, otherwise every few days, until the skull reaches the normal size. When there is a negative pressure and especially if the bones remain separated after the evacuation, compression should be employed. Lumbar puncture is to be employed, if the skull is open, only in mild cases, or in severe cases when a considerable improvement has followed ventricular puncture, and the removal of a greater quantity cannot be undertaken. The more advanced the closure of the skull, so much more careful should one be, especially with associated negative pressure. One must proceed very carefully in closed skulls, in order to avoid completely negative pressure or a marked decrease of increased pressure, at one sitting. One should desist frequently and every time withdraw less. Then the lumbar puncture should be employed. If this is not successful, repeated ventricular punctures should be made through a small trephine opening, best in the frontal region. The complicated methods of operation should not be attempted in an open or closed skull until repeated and energetic punctures have been tried and have failed to accomplish their purpose.

Six Cases of Hypogastric Retrograde Catheterization.—HACHE (*Ann. d. mal. a. org. gen-urin.*, 1910, 1, 233) did retrograde catheterization in six cases. In the first case there was an old fracture of the pelvis, with a splinter of the pubis situated along the urethra between two strictures. An external urethrotomy was performed, a hypogastric incision becoming necessary for retrograde catheterization. An internal urethrotomy was also necessary. In the second case urinary extravasation resulted from an old stricture, with an impacted calculus in the urethra. Besides the hypogastric catheterization an internal urethrotomy was performed. In the third case there was a fracture

of the pelvis with a laceration of the prostatic urethra and a tear of the rectum. Infiltration of urine resulted, calling for an external urethrotomy and retrograde catheterization. In the fourth patient an insuperable gonorrhœal stricture called for retrograde catheterization and an internal urethrotomy, and in the fifth, in which the same condition was present and the same treatment carried out, the union in the bladder and urethral wounds was immediate and the stricture rapidly recurred. In the sixth case, a tight stricture was treated first by internal urethrotomy, then by external urethrotomy, and forty-five days later a hypogastric retrograde catheterization was necessary. He emphasizes the absurdity of the diagnosis of a foreign body in the urethra in connection with the first case owing to the few symptoms present; the difficulty one may experience in opening the empty bladder for retrograde catheterization; and the repair of the urethra after trauma or operation. The method of finding the urethra through the perineum posterior to the lesion, at the apex of the prostate, is more inconvenient and laborious than by the hypogastric and bladder route.

The Treatment of Dry Arthritis with Injections of Vaseline.—ROVSING (*Annals of Surgery*, 1909, l, 1052) has injected 53 joints with vaseline, but bases his conclusions on the results of 35 of these in 30 patients. He has been able to control the results at least eighteen months. These cases he divides into two main groups, of which the first, consisting of 7 cases, comprises the non-traumatic "dry" arthritis, is of rheumatic, uratic or unknown origin; while the last group comprises the traumatic dry arthritis, into which comes the senile disorder, together with 4 cases in which vaseline has been injected in order to prevent ankylosis after arthrotomy and arthrectomy—23 in all. The result of his experiments with the injection of vaseline in the cases of really chronic apparently dry arthritis of uratic, rheumatic, or other infectious origin was as follows: If by the puncture fluid is found in the joint, one ought to abstain from the vaseline treatment completely; if, however, the joint is found completely dry and the inflammation apparently extinct, one ought to attempt the injection of a smaller quantity of vaseline, which cannot distend or strain the capsule, afterward watching any possible return of the symptoms of inflammation. In two of the non-traumatic cases, finally, a good functional result was obtained. In the traumatic cases the results were almost constantly satisfactory. The injection should be made under absolutely aseptic precautions, and the quantity injected should vary with the size of the joint. Considerable experimentation was necessary in deciding for each joint the necessary quantity. In adults the hip will take without difficulty, 20 to 25 c.c; the knee, 10 to 12, and 15 at the most; and in the shoulder, 15 c.c. will be suitable, as a rule.

Principles of a Radical Treatment for Proctosigmoiditis.—BASTIANELLI (*Annals of Surgery*, 1909, 1095) has in recent years, seen a relatively large number of these cases, commonly called strictures of the rectum, but which really involved greater problems than those connected with a simple stricture. Prominent among the anatomical conditions to be considered in the treatment is not the stricture itself but the inflamma-

tion of the rectum and its extent, since the stricture is a limited consequence only, not the essential disease; so that if we succeed in removing only the strictured part we have done nothing at all in the majority of cases, the inflammation being still there with all its actual symptoms and promise of a new stricture in the future. An exploratory laparotomy is necessary for examination of the intestine as a preliminary to the radical treatment. This will permit the establishment of an artificial anus, which will give the inflammed parts a long period of rest, and thus the patient an opportunity to recuperate from his poorly nourished, emaciated, and often, cachectic condition. The artificial anus is also a safety valve allowing aseptic operating and a clean after treatment. The radical operation will now follow, and it will be guided by what the preliminary exploration has ascertained. If the lesion is a limited one, a perineal extirpation may be performed; if extensive, resort must be had to a combined abdominal and perineal operation, in both cases the aim being to preserve the function of the sphincter and to put into it a healthy portion of bowel. In stricturing proctitis or proctosigmoiditis, therefore, the treatment should be: (1) Cecal anus and laparotomic exploration of the bowel. (2) Perineal or combined removal of the diseased section in one or two stages, with mobilization of the sigmoid and colon if necessary, and preservation of sphincter. (3) Closure of the cecal anus. (4) Plastic operation if necessary. Bastianelli emphasizes the importance of resorting more frequently to the abdominal route in the treatment of stricture of the rectum for the purpose of preliminary exploration, and the importance of exact ligating and cutting the arterial supply from the abdomen, even in cases of perineal operation, to prevent any damage to the circulation.

Intestinal Obstruction in Children.—Alapy (*Archiv. f. klin. Chir.* 1910, xcl, 803) reports the results of his observations on 45 personally observed cases of intestinal obstruction in children. The ages of the patients varied from that of a nursing infant to fourteen years. Intestinal obstruction is more readily recognized in children than in adults. In children, it is generally due to two pathological conditions, appendicitis and invagination. In Alapy's 45 cases, there were only 5 which were not due to one or the other. Those due to appendicitis were observed in ten different forms; dynamic ileus of acute inflammation, adhesive ileus of acute inflammation, strangulation after the disappearance of the acute stage, early form of postoperative adhesion ileus, late form of the same, occlusion from progressive peritonitis, from abscess in Douglas' pouch, reflex (spastic) obstruction, obstruction from a strangulated or inflammed appendix in a hernial sac, and ileus in consequence of a diffused peritonitis. On the other hand, the invagination group were uniform. Whether the cause was the same or different, the clinical picture was nearly the same. It is best not to concern oneself with an unsatisfactory classification. From case to case an effort should be made to establish an exact diagnosis concerning two points; (*a*) the pathological process involved, and (*b*) the site of the obstruction (not the portion of intestine involved but of the abdomen). One of the most important features is the presence or absence of tension of the abdominal wall. The absence

of this sign in all of Alapy's cases of invagination was of the greatest diagnostic importance in the differentiation from appendicitis. The treatment of intestinal obstruction in children differs in certain respects from that in adults. A rapid and sparing operation is often necessary to save life. Selfevidently, it must be applied to the pathological process present. Under similar circumstances, enterostomy has a wider range of usefulness than in adults. This is not merely a palliative operation. With two exceptions all the children who survived enterostomy, were radically cured. The effort to cure should be made not through resection but through disinvagination. Resection is only exceptionally necessary, and should be done only after disinvagination has been accomplished. The very frequent assertions that the attempts to disinvaginate fail because of the presence of adhesions, are based upon error. The cause of the failure is not adhesions, but a faulty technique. Alapy succeeded in disinvaginating all cases of ileocecal invagination. Firm adhesions were practically never present. The method of disinvagination was as follows: The anal end of the intestinal tumor is grasped in the fist and squeezed without shifting the hand from its place. If the oral end is kept in view, a small portion of the invagination at the neck can be seen emerging. The hand should now grasp a higher portion, again at the anal end of the mass, and the procedure should be repeated until the disinvagination is completed, In many forms of intestinal obstruction, an attempt at non-operative reduction is justified, provided the obstruction has not lasted long. It must be overcome quickly. The resistance of the child is less than that of the adult. Delay of operation is fatal. If a brief trial with non-operative reduction fails, operation should be done immediately.

THERAPEUTICS.

UNDER THE CHARGE OF

SAMUEL W. LAMBERT, M.D.,

PROFESSOR OF APPLIED THERAPEUTICS IN THE COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK.

General Principles of Tuberculin Diagnosis and Treatment.—BALDWIN (*Jour. Amer. Med. Assoc.*, 1910, liv, 260) says that the therapeutic use of tuberculin may have two fairly definite objects in view: One is to diminish the sensitiveness to the toxin—that is, to itself; the other is to cause intermittent local reactions, and thus to stimulate the disease focus to heal or become absorbed. The possibility of the production of a recognizable immunity to the disease thus far by any form of tuberculin treatment is open to question. A certain degree of resistance is indirectly accomplished when sensitiveness to tuberculin is decreased to a marked degree, accompanied by constitutional improvement. The degree of tolerance or immunity to tuberculin is proportionate to the dose that can be borne without reaction. Hence the progressive increase of dosage

is essential. When only reactions about the focus of disease are desired the dosage need not be increased so long as sensitiveness persists to small doses. As soon as this sensitiveness is overcome the treatment should be interrupted until sensitiveness returns, or the doses must be increased to an unwise degree. Baldwin says that only patients in a quiescent state of the disease are likely to be benefited. Pulmonary patients should be in a good nutritive condition and free from persistent fever over 100°, hemoptyses, night sweats, chronic diarrhœa, or extensive laryngeal complications. The physical signs in the lungs should indicate a localized disease, free from large pneumonic consolidation or disseminated disease. Progressive tuberculosis of any form is a contraindication to this treatment. Reactions are to be avoided, and may involve danger when repeated, except in cases of well-arrested localized disease. Slight unperceived focal reactions probably occur under any plan of tuberculin treatment, and, when rightly timed, are beneficial. The author points out the obvious fact that focal reactions can be best observed and applied with safety in those cases of skin, bone, joint, or genito-urinary tuberculosis in which the lung is not involved. With reference to the choice of tuberculin, Baldwin says that opinions are too variant to permit the formulation of rules. In general the dosage is more controllable with solutions, and reactions are less frequent from emulsions. However, the absorption of emulsions is very uncertain, and reactions may occur unexpectedly with the increase in dosage. Therefore he believes that the solutions are safer for tuberculin immunization. The dosage is empirical and entirely dependent upon the individual case. The clinical symptoms are the most satisfactory guides, though opsonic determinations may be of value in the hands of experts. For the majority, the opsonic index is impracticable and misleading. Tuberculin should be administered subcutaneously. Tuberculin when given by the mouth or rectum is too uncertain of absorption to warrant any recommendation. Baldwin concludes by saying that the technique of tuberculin injections, the guide to correct dosage and intervals, are details which vary with the preparation used and the experience of different observers.

Total Energy Requirement in Diabetes Mellitus.—Du Bois and Veeder, (*Arch. Int. Med.*, 1910, v, 37), upon the basis of a series of careful experiments, believe that the total energy requirement of diabetes does not vary so markedly from the normal as some other observers have maintained. They state that, in addition to the 31 to 35 calories per kilo required for the normal individual, only enough extra calories should be given to the diabetic to cover the loss of sugar in the urine. If this is not done the body protein and fat are broken down to supply the needed amount.

The Dietetic Treatment of Diabetes Insipidus.—Schuetz (*Berl. klin. Woch.*, 1909, xlviii, 2168) reports a case of diabetes insipidus treated with a salt-poor diet. The patient had lost thirty-five pounds, and that was his chief symptom. The daily amount of water ingested was at times over 40 liters. Before treatment the daily amount of urine was from 18 to 20 liters, with a specific gravity of from 1000.5 to 1001, with a sodium chloride content of from 32 to 34 grams and a total nitrogen of

from 22 to 23 grams. All mineral waters were forbidden and a salt-poor diet with a minimum of protein was ordered. The daily quantity of urine fell to from 6 to 8 liters daily, with a specific gravity of from 1002 to 1003. The sodium chloride content fell to 12.9, and coincidently there was a great improvement as regards thirst. During six months the patient gained twenty-six pounds, with a marked improvement in the general condition.

Treatment of Diabetes Insipidus.—MINKOWSKI (*Therapie d. Gegenwart*, 1910, i, 4) says that the daily amount of the urine in diabetes insipidus is at times dependent upon the amount of sodium chloride in the food. He advises the determination of the chloride content and specific gravity of the urine after the ingestion of a considerable amount of salt. If the specific gravity and chloride content increase relatively more than the amount of the urine, the power of concentration is still retained. Such cases are benefited by a restriction of the amount of fluids. On the other hand, if the dose of salt influences the amount of urine more than the chloride content, a diminution of the sodium chloride and the nitrogen in the diet is indicated. If no benefit results from the withdrawal of salt, Minkowski believes that the trouble is then probably due to some organic lesion of the nervous system. On the assumption that such organic disease is the result of syphilis, antisyphilitic treatment may prove of value.

Notes Respecting the Dietary of Goutily Disposed Persons.—DUCKWORTH (*Pract.*, 1909, i, 1) says that in the treatment of gout the mistake is often made of treating according to system and of not considering the individual case. He believes, for instance, that there is no rule applicable to all gouty persons with reference to their allowance of meat. In general, meat in moderation is in no way harmful, but beneficial. Strong meat soups and beef extracts are to be avoided; pickled or salt meats are, as a rule, inadvisable, but they need not be absolutely excluded from the diet. He believes that meat should be roasted or broiled, that mutton is better than beef and much better than poultry for the average case. Liver, sweetbreads, and kidney should not be allowed. A purin-free diet works very well in many cases of gout. However, there are patients who cannot bear this diet long. Fish and some shell fish, if eaten fresh, are considered by Duckworth to be harmless. He allows ordinary bread, plain or toasted, or plain biscuits. He believes that plainly cooked potatoes are entirely harmless. Green vegetables, especially spinach, cress, and lettuce are of value. Asparagus should be given very sparingly. Fruits, both cooked and raw, may be given to gouty patients. Tea, coffee, and cocoa have no bad effects, with the exception of strong black coffee taken after meals, which he prohibits. A single wine in small quantity, preferably port, Bordeaux, or champagne, is allowed. He especially forbids large mixed meals of animal and farinaceous food elaborately prepared and richly seasoned. He forbids cooked tomatoes, rhubarb, and food cooked with fat or sugar. Sauces, relishes, and highly spiced food must be avoided. He believes that both lemon juice and vinegar are harmful. Mustard and salt may be taken in moderation. Abundant water should be given to gouty patients, and should contain little calcium or iron. He says that the continued use

of alkaline or lithia drinks often is harmful and should be forbidden. In general, Duckworth lays more stress upon the quantity of the food and the manner of its preparation, which should be simple, than upon a strict limitation of its character.

Flatulence and its Treatment.—Boas (*Berlin. klin. Woch.*, 1910, iii, 89) divides flatulence into several varieties, with corresponding differences in its treatment. One form, which he denotes as exogenous, is due to intake of gas while eating, and is usually observed in rapid eaters. A second form, associated with colicky pain and which he denotes as endogenous, occurs as a result of chronic constipation or inflammatory conditions of the small and large intestines. In this class may also be included the flatulence resulting from organic or less often functional spasmodic stricture of the intestine. Finally, passive congestion often is the cause of intestinal flatulence. Boas deprecates the treatment of flatulence by carminatives, and advises a rational treatment dependent upon the etiology. For the treatment of flatulence of alimentary origin, especially when associated with chronic constipation and catarrhal inflammation, the most important factor in the treatment is the exclusion of fermentable foods from the diet. Since individuals differ markedly with respect to their digestion of different foods, their tolerance for various foods must first be determined. Boas mentions milk, buttermilk, eggs, and rare meats among the foods most apt to result in fermentation. He lays particular stress upon the avoidance of raw or rare meats. Potatoes are also responsible for flatulence in individual cases. He considers magnesium salicylate, in doses of from 1 to 2 grams three times a day, the best antifermentative drug, and he says that it has the further advantage of not causing constipation. Boas advises small repeated doses of castor oil when constipation is associated with the flatulence. Surgical treatment alone is of value in the treatment of flatulence due to organic stricture. When the flatulence is due to passive congestion, cardiac tonics and diuretics are indicated.

PEDIATRICS.

UNDER THE CHARGE OF

LOUIS STARR, M.D., AND THOMPSON S. WESTCOTT, M.D.,
OF PHILADELPHIA.

The Regulation of Fat Percentages in Infant Feeding.—A. S. Bleyer (*Archives of Pediatrics*, 1910, xxvii) has made observations of the feeding in 600 infants, with special attention to the fats. He found that when the fats were reduced to less than 1 per cent. the child became very hungry, regardless of a reasonable increase of proteins. This effect was noticed whenever it was tried. The effect of fat-free feeding on the intervals of feeding, shows that a normal child will be hungry in about an hour and a half, and that the number of feedings depend in

great measure on the percentage of fat in the mixture. From a study of the influence of fats on vomiting, Bleyer concludes that the caseins offer little difficulty in vomiting in babies, if the fats do not interfere, and that the teaching on the formation and indigestibility of casein curds has been incorrect. A series of vomiting babies was selected in which sodium citrate had controlled the vomiting. The fats were then removed from the feedings and the sodium citrate discontinued. In the majority of cases the vomiting did not recur. He, therefore, concluded that a rapid precipitation of caseins did not often cause vomiting in the absence of fats. Again, if whole milk is precipitated, over 60 per cent. of the curd by bulk is fat. Furthermore, the curd is tough, leathery, and tenacious, which characteristics are never found in a simple casein curd without fat.

On the influence of fats on the character of the stools and on constipation, he reports 28 records kept of babies fed on a low fat percentage, in 20 of which there was at least one stool every day and a number had diarrhœa. Aside from these records, he has observed usually two or more stools a day in children on a low fat percentage. The foul odor in a few of the diarrhœa cases was at first thought to be due to decomposition of the ingested proteins. However, he quotes Feer and Finkelstein, who have shown that almost none of the ingested proteins is found in the stools, and insist that the odor is due to the putrefaction of mucous and intestinal secretions and that the protein in the stools is derived from the nucleoproteins of the bile and the intestinal secretions.

The Condition of the Blood in Rickets.—LEONARD FINDLAY (*Brit. Med. Jour.*, 1910, I) studied the condition of the blood in rickets in children and also in puppies in which he had induced rickets experimentally. In 30 cases of active and uncomplicated rickets in children between twelve and fourteen months of age, only 9 showed any degree of anemia. In 2 of these the hemoglobin was only 5 per cent. below the accepted average, and the red cells in no instance were less than 4,100,000 per cubic millimeter. The majority of cases, on the other hand, gave high blood estimations so far as the hemoglobin and the number of red cells were concerned. Nucleated red corpuscles were seen on only one occasion. In only 2 cases was there an unequivocable leukocytosis, the white cells numbering 20,000 to 30,000 per cubic millimeter. Of the other 28 cases, 9 gave a normal or subnormal estimation, and in 19 the leukocytes were moderately increased in number, the maximum being 19,000 per cubic millimeter. Differential counts showed nothing characteristic. The results of the observations in experimental rickets in puppies were in entire accordance with those obtained in spontaneous rickets in children. When anemia was found it was minor in degree and was usually accounted for by some complication. Leukocytosis when present was also moderate and could usually be explained by some complication.

Intraventricular Injection of Flexner's Serum for Cerebrospinal Meningitis.—LOUIS FISCHER (*Monthly Cycloped. and Med. Bulletin*, 1910, iii) reports a case of cerebrospinal meningitis in an infant, aged two months, which was treated by intraventricular injections of Flexner's

antimeningitis serum, with complete recovery. This method has so far not been successful in cases reported by Cushing, Netter, and others. The chief symptoms in the child were sudden onset with vomiting, rigidity of the head, neck, and extremities, and convulsive movements. The anterior fontanelle was open one-half inch and slightly bulging. On October 2, the first lumbar puncture resulted in 1 c.c. of turbid, blood-stained fluid which showed no meningococcus microscopically. The next three lumbar punctures resulted in dry taps, and as the fever, rigidity, opisthotonos and twitching were marked, the infant's lateral ventricles were tapped (October 20) and 15 c.c. of turbid fluid containing pus were withdrawn from the right ventricle. Smears taken from this fluid showed intracellular, Gram-negative meningococci. The ventricles were irrigated with normal saline solution at a temperature of 105° F. The excess fluid was drained out through the needle and 25 c.c. of Flexner's antimeningitis serum slowly injected into the ventricles. The infant changed in color from a waxy pallor to a uniform red flush all over the body, which persisted over half an hour with profuse perspiration. The temperature was 101° F., the respirations 80, and the pulse 120. On October 21 the ventricles were again irrigated, and 20 c.c. of the serum were injected. On October 22 the condition of the child was very poor. Opisthotonus was marked, and frequent paroxysms of muscular contractions occurred involving all its limbs. On October 23 a puncture below the fourth lumbar vertebra resulted in a dry tap. A second needle was inserted below the third lumbar vertebra and 15 c.c. of Flexner's serum injected through it, 3 c.c. returning through the first needle. Of 15 c.c. of serum then injected through the first needle, 5 c.c. returned through the second needle, showing that both needles were in the canal. In all, the infant retained about 25 c.c. of the serum in the spinal canal. A better result seemed to be obtained by using both the intraventricular method and the injections into the spinal canal. On October 25, 5 c.c. of slightly cloudy fluid was obtained by lumbar puncture. No meningococci were found in it, and 15 c.c. of the serum was injected into the spinal canal. On October 27, 20 c.c. of the serum was injected into the ventricles, although no fluid could be withdrawn. The total amount of Flexner's serum injected was about 105 c.c. The infant improved steadily from now on. On November 22, the right lateral ventricle was aspirated and 50 c.c. of clear fluid withdrawn which contained no meningococci and which resembled hydrocephalic fluid. The infant recovered without any complication on December 16. Fischer believes that if the ventricles cannot be drained by lumbar puncture, owing to a stasis or walling-in of ventricular or purulent fluid, and the symptoms persist, then the only way left is to tap the ventricles, flush with normal saline solution, and inject the antimeningitis serum as a specific. No danger was incurred in his case by piercing the frontal lobe and entering the ventricle, but rather relief was given to the symptoms of intracranial pressure. Flexner warns against injecting more fluid, that is, serum, than has been removed. The ventricles are aspirated in an infant through the anterior fontanelle. In older children the Kocher method is used, entering the skull by an incision over the second frontal convolution, and through it aspirating the ventricle.

The Early Diagnosis of Infantile Scorbutus.—Henry Koplik (*Archiv of Diagnosis*, 1909, ii) states that scorbutus may develop in any infant whose food is or has been constructed on denutritional lines. It is a mistake to reject the possibility of scorbutus in a patient fed upon the breast or raw milk, since breast milk may have a denutritional composition, and raw milk be given in a denutritional state. Another element in the etiology of scorbutus is its intestinal source. The metabolism having become deranged, a development and invasion of toxins through the gut probably adds to the symptom complex. The ingestion of sterilized food in itself cannot explain all the phenomena of the disease, and many infants take sterilized food without developing scorbutus. The disease is uncommon in infants under five months. The first signs of incipient scorbutus are, a mild form of anemia, pain in the joints or bones elicited only by pressure, and the appearance of blood in the excretions or in the vicinity of bones or periosteum. In an otherwise perfectly healthy infant, fed on pasteurized milk, hematuria was the only gross symptom. Closer examination revealed a very mild anemia, a slight line of redness along the gums, and tenderness of the tibiæ only on deep pressure. Antiscorbutic treatment rapidly cleared up these symptoms, which otherwise would have developed a full picture of scorbutus. An infant, aged eleven months, was placed on a raw milk mixture containing excessive fat (7 per cent.). It gained satisfactorily until it developed a slight temperature above normal, a slight tenderness on manipulation of the left thigh and leg. The teeth and gums were normal except that there was a small, bluish-red cushion over the situation of the left lower canine, no tooth being felt. A diagnosis of osteomyelitis had been made, there being a high leukocyte count. The diagnosis was scorbutus (due to the excess of fat in the food), causing the pain in the thigh and hemorrhage in the left canine tooth-sac. Upon a proper food the infant made a complete recovery. It is not uncommon in infants of about six months who are apparently thriving, to find tenderness over the tibiæ on deep pressure. Such infants may have rickets, but the tenderness in question is scorbutic, and the test of correctness of the supposition is the rapid response to a change of diet aimed at warding off a full development of scorbutus.

GYNECOLOGY.

UNDER THE CHARGE OF

J. WESLEY BOVÉE, M.D.,

PROFESSOR OF GYNECOLOGY IN THE GEORGE WASHINGTON UNIVERSITY, WASHINGTON, D. C.

Spontaneous Rupture of Pyosalpinx into the General Peritoneal Cavity Producing Acute Diffuse Peritonitis.—Bonney (*Surg., Gyn., and Obst.*, 1909, ix, 542) has quite carefully studied the literature of this subject and from this study has concluded that: Spontaneous rupture of a

pyosalpinx or tubo-ovarian abscess into the general peritoneal cavity, producing acute fulminating peritonitis is a very rare accident. In the severity of its symptoms it usually resembles other forms of perforative peritonitis. It conforms to the general rule obtaining in such cases, that the earlier operation is performed, the greater is the chance of recovery. It is a very momentous accident, having a mortality of 30 per cent., even in those cases in which operation is made during the first twelve hours. It should be considered as the possible causative agent in all cases of acute general peritonitis of obscure origin occurring in females. Its proper treatment is immediate operation.

The Later Results of Ovariotomy.—HOFMEIER (*Surg., Gyn., and Obst.*, 1909, ix, 381) carefully discussed the later results of ovariotomy, giving each pathological condition careful, though not exhaustive, consideration. Hofmeier believes fully 5 per cent. of ovarian carcinomas are secondary. He has operated on 59 cases of the ovary, in 43 of which but one ovary was involved. In 22 of the latter the affected ovary only was removed. The first of these is living, eighteen years after the operation. She bore a child one year after the operation and is now forty-five years of age. While Hofmeier believes operation should be performed in all cases in which removal seems possible, yet in unilateral involvement he recommends leaving the second ovary in young women. If both ovaries are involved, and then only, is removal of the uterus recommended. [Hofmeier's statistics in operation for cancer of the ovary are better than those of this country.—J. W. B.]

Abdominal Myomectomy for Large Uterine Fibroids.—KUHN and FRICK (*Amer. Jour. Obst.*, 1909, lx, 443), after discussing the literature of hysterectomy and myomectomy for fibroids of the uterus, reports a series of ten successful myomectomies. In this paper are drawn the conclusions: (1) That myomectomy is especially indicated in women under forty years of age in which the genital tract can be left intact; (2) the limits of myomectomy should be extended under proper technique to cover part of the field of supravaginal hysterectomy; and, (3) myomectomy is the operation of choice for fibroids of the lower uterine segment in pregnancy.

Hemorrhagic Uteri; Myopathic Uterine Hemorrhage.—B. H. ANSPACH (*Surg., Gyn., and Obst.*, 1909, ix, 315) believes the arteriosclerosis to which the terms "apoplexia uteri" and "intractable hemorrhage" have been applied is nothing more than a normal sclerosis and obliteration of the vascular channels of the uterus occurring in due proportion to the parity and the age of the individual. In only two of the cases reported in the literature or collected by Anspach were the uterine arteries calcified in a woman who had not passed the meopause. In these two exceptions the patients had reached the usual age for the occurrence of the menopause. The normal atrophy of the uterus, which begins about the time of the menopause, affects the muscle a little more than it does the connective tissue, but this plays no part in producing hemorrhage. Anspach believes the hemorrhages in conditions of this kind are due to fungous endometritis, hypertrophied and cystic cervix, displacement of the uterus, inflammatory lesions of the

adnexa or the cellular tissue of the pelvis, or congestion of the pelvic bloodvessels from general weakness, cardiac or renal disease.

The Air of the Operation Room as a Possible Factor in the Infection of Wounds.—H. ROBB (*Amer. Jour. Obst.*, 1909. lx, 451) has conducted a series of experiments to determine the relative infectivity of the air in his gynecological operating room in the Lakeside Hospital under varied conditions. The experiments were made in five series: (1) The floor was washed with a 1 to 1000 corrosive sublimate solution; (2) the washing was done with 1 to 20 carbolic acid solution; (3)with plain water; (4) no preparation of the floor was made; and (5) the series was composed of observations in other rooms and without any preparation of the floor. The use and non-use of a fan was also a feature of every series. Robb concludes that the use of antiseptics on the floor markedly lessened the number of bacteria in the air. More notable was the effect of the degree of cleanliness of the walls of the room. The effect of the fan was concluded to be nearly a negligible matter.

Advantage of the Combined Intra- and Extraperitoneal Ureterolithotomy for the Removal of Stones from the Lower Ureter.—JONAS (*Amer. Jour. Obst.*, 1909, lx, 728) believes the proper treatment for stone in the lower ureter is the combined intraperitoneal and extraperitoneal ureterolithotomy. The intraperitoneal part of the operation serves for exploration and for the removal of conditions which are possible etiological factors in the lodging and formation of stones. It also frequently makes the finding of the stone easier. The extraperitoneal steps serve for the removal of the stone. Stones higher up, at the crossing of the ureter and the iliac vessels can be removed by this combined route, as described and first emphasized by Gibbons. Should it be difficult to push the peritoneum back far enough, it might become necessary to add McBurney's gridiron incision. In this way, a flap is formed which gives complete access to the whole ureter from its point of crossing with the iliac vessels to the bladder. The shape of the entire incision is analogous to the cut described by Fowler for the extraperitoneal removal of ureteral stones in the lower ureter and now frequently advocated for the ligation of the common iliac artery.

OTOLOGY.

UNDER THE CHARGE OF

CLARENCE J. BLAKE, M.D.,

PROFESSOR OF OTOLOGY IN THE HARVARD MEDICAL SCHOOL, BOSTON.

The Ultimate Results of the Conservative Treatment of Chronic Suppurative Middle-ear Disease.—VOGT (*Ztschr. f. Ohrenheilkunde*, 1909, lviii, 288).—The author's report is based upon the observation of 148 cases at least two and one-half years after cessation of treatment, those cases only being recorded as healed in which the discharge had entirely

ceased. The treatment, in the simple middle-ear cases included cleansing by means of normal salt solution followed by careful drying, removal of secretion by suction, the use of 10 per cent. boroglycerin, for the softening of the crusts, endonasal treatment, middle-ear irrigation through the tympanopharyngeal tube, in some cases ossiculectomy, instillation of solution of boric acid in alcohol with glycerin or of sublimate, touching with silver nitrate, and the insufflation of boric acid. In the cases with suppuration in the epitympanum the middle-ear syringe was used, and in all cases when indicated due attention was given to hygiene and to general medication. Of the 90 cases of simple suppurative middle-ear disease, 34 were healed and had so remained up to the time of observation; there had been 9 relapses, 32 had been improved, and 15 were unhealed. Of the 58 epitympanic cases, 23 were healed, there were 5 relapses, 21 were improved, and 9 were unhealed.

Quantitative Determination of Caloric Nystagmus in the Normal Labyrinth.—KIPROFF (*Passows Beiträge*, 1909, ii, 129).—In order definitely to test the increase or decrease of excitability of the vestibular end apparatus, the determination of the vestibular reaction, in patients with normal labyrinths, was undertaken by the author by irrigation of the ear with water of a temperature of 86° F., the patient looking fixedly in a direction opposite to that of the irrigated ear, and the moment noted when the nystagmus began. This notation was effected by means of a stop watch started at the moment of commencement of irrigation, the moment when the nystagmus began being noted and the patient then directed to look straight forward, the moment of recurrence of the nystagmus being again noted, the irrigation being then immediately stopped, and a further time note made of the duration of the nystagmus, to the point of its complete disappearance. As the result of this examination, in 34 cases, a duration of irrigation, under the above-named conditions, with the eyes directed away from the irrigated ear, of from 15″ to 45″ was sufficient to induce nystagmus, but the investigation was continued also in cases both of non-suppurative and of suppurative middle-ear disease, in cases of total destruction of the drum head, of middle-ear suppuration after the radical operation, in inflammation of the external auditory canal, and in acute disease of the middle ear with the following results: The nystagmus symptoms appeared most speedily in the cases of total defect of the drum-head, with epidermatization of the labyrinth wall and in the cases which had undergone the radical operation; next in order came the normal cases, then the chronic suppurative cases, and finally, the acute suppurative and the cases of inflammation of the external canal. The average duration of the nystagmus was, in the normal and in the acute cases, from 1′, 55″ to 3′, 5″; in the chronic suppurative and in the healed cases from 1′, 25″ to 2′, 45″.

Otosclerosis.—THEODOR HEIMANN (*Sixteenth International Medical Congress*, Budapest, 1909, p. 183).—The conclusions drawn by the author, at the end of a long, carefully studied and critically presented tstaement of the present knowledge upon this subject, to which his now personal investigations have largely contributed, are as follows:

(1) The structural basis of the so-called otosclerosis consists in a bony ankylosis of the stapediovestibular joint. (2) From the anatomical pathological investigations so far made it would seem probable that the fixation of the stapes is the result of an inflammatory process of individual origin, which, while primarily it may have included the whole, or a large part, of the tympanic mucosa, has specially localized itself in the neighborhood of the labyrinth window. (3) While, from the observations thus far made, the supposition of a primary osteitis of the labyrinth capsule exhibiting itself in the region of the stapes cannot be excluded, the grounds for such a conception are not entirely conclusive, and do not sufficiently explain the considerable and progressive disturbance of hearing, without participation of the stapediovestibular articulation or the terminal nerve-ending apparatus of the labyrinth. (4) The sole and important cause of the disturbance of hearing, and other symptoms, in the so-called otosclerosis is a fixation of the stapes in the oval window, without differentiation as to the means by which this condition is brought about, whether originating in the middle ear, in the labyrinth, or existing as a congenital defect. (5) The principal cause of the otosclerosis must be regarded as a disturbance of general nutrition without reference to its origin. (6) Previous experience shows that heredity, anemia, syphilis, gestation, advanced age, and the female sex especially dispose to this disease, the cause of which in many cases remains unexplained. (7) Long and careful investigation would be required to determine whether or not this disease is dependent upon local causes, such as diseases of the upper respiratory tract, and particularly of the nose and nasopharynx. (8) The otosclerosis is to be regarded as the localization effect of a general disturbance of nutrition, evidencing itself in the ear. (9) The clinical picture of otosclerosis has, in certain cases, a strong resemblance to that occurring in the adhesive processes, of which fixation of the stapes is an accompaniment. (10) A definite therapeutic effect can be attained only by general treatment; local treatment is ineffective in the true primary cases of otosclerosis. (11) The expression otosclerosis, which corresponds neither to the structural nor to the clinical picture of this disease, and is liable to lead to misunderstanding, should be, with the corresponding term, "dry middle-ear catarrh," absolutely abandoned, and the title "periostitis ossificans stapediovestibularis" substituted for it. (12) Should further investigation determine that the disease originates primarily in the labyrinth capsule and is of inflammatory origin, the term "Ostitis vascularis stapediovestibularis" would be preferable.

HYGIENE AND PUBLIC HEALTH.

UNDER THE CHARGE OF
VICTOR C. VAUGHAN, M.D,
PROFESSOR OF HYGIENE IN THE UNIVERSITY OF MICHIGAN, ANN ARBOR.

Vaccine Immunity.—SÜPFLE (*Archiv f. Hygiene,* 1910, lxviii, 301) closes an investigation of this subject with the following conclusions: (1) The local insertion of a vaccine results in only a local reproduction of the virus. (2) Immunity results from the gradual extension of the effects of the virus from the point of inoculation. (3) This immunity is histogenetic. (4) Cutaneous immunity results from either subcutaneous or intravenous vaccination. (5) Lymph heated to 60° induces, though not constantly, a cutaneous immunity. (6) When lymph is dialyzed, one obtains a dyalysate which, when introduced subcutaneously, induces in many instances a partial immunity to subsequent cutaneous vaccination. (7) After cutaneous, subcutaneous, or intravenous inoculation the blood serum, sometimes, not constantly, contains antibodies which are capable of destroying the virus.

The Poisonous Effects of Sodium Sulphite.—KIONKA (*Archiv f. Hygiene,* lxvii) found that continued feeding of small animals with moderate doses of sodium sulphite had no recognizable effect upon their growth or health, but after death he found many hemorrhagic spots in various organs and tissues. He killed his animals by washing out the blood-vessels with a dilute solution of indigocarmin. With the heart beating this coloring matter is supposed to be carried to all the tissues, but fails to reach any portions cut off by rupture of a vessel. On the other hand, hemorrhages would be recognized as dark blue spots. Lehmann and Trautwein (Ibid., 68) have gone over this work, but suspecting that the hemorrhages might be due to the mode of death, killed their animals with chloroform slowly administered so as to avoid a death struggle. The animals employed were cats and dogs. The amount varied from 15 to 30 mg. per kilo per day, and the feeding was continued for two hundred days. The animals took the food containing the sulphite readily, grew normally, and at the end of the period appeared in perfect health. When killed no lesion, either macroscopic or microscopic, attributable to the sulphite, could be detected. The doses given were equivalent to from 3.7 to 18.7 grams of pure crystalline sodium sulphite per day to a man of 75 kilos. These investigators conclude that moderate amounts of sulphite may be absorbed from the stomach, oxidized to sulphate, and eliminated without harm to the individual. They are, however, careful to state that this finding should not be interpreted as supplying any justification of the use of sulphite as a preservative in meat. Sulphite is used as a preservative for chopped meats, such as the so-called Hamburger steaks, because it restores the color to putrid bits that could not be sold without this sophistication. This is the real and truly valid objections to its use.

Nickel Utensils.—LEHMANN (*Archiv. f. Hygiene,* lxviii, 421) has investigated the possibility of poisoning from cooking utensils made of nickel. Whether we will or not, we do get more or less of the widely distributed metals, as iron and copper, in our food, but this is not true of nickel. Some foods do take up small quantities of nickel when prepared in vessels made of this metal. Lehmann finds that if all the food eaten by a man be prepared in nickel he might get a maximum of 2 milligrams of the metal per kilo of body weight per day, and from his experiments on cats and dogs he concludes that this would do no harm.

Pseudomeningococci in the Throats of Healthy Children.—In 8 per cent. of 150 school children examined, LIEBERKNECHT (*Archiv f. Hygiene,* lxviii, 443) found pseudomeningococci. None of these children had been exposed to meningitis. With one exception, none of these organisms could be distinguished by cultural methods from the real meningococcus. This one gave a yellow growth on potato. At a temperature of 55° and after twenty-four hours they were agglutinated by specific serum in high dilution, while the serum of a normal rabbit had no effect, 1 to 20. On saccharine media these growths cannot be distinguished from the real. They grow well in pure culture on placental agar and in blood serum. On the addition of hematin to normal agar they grow abundantly and retain their vitality for a month. The addition of the saccharate of iron to ordinary or placental agar improves the growth on these media satisfactorily at either room or blood temperature.

On Being Tired.—BRUNTON (*Practitioner,* lxxxiii, 409) discusses fatigue under the above title in his usual charming style. He seems inclined to the theory of Weichardt of fatigue toxins and antitoxins. However, he refers to the well-known custom of Alpine guides to prevent or relieve fatigue by taking food every two hours, and he thinks that the effect of food in relieving fatigue is so rapid that there is not time for absorption of the food, and that the action is an indirect one. The chemistry of the fatigue toxins has not been determined, but Brunton thinks them allied to ammonia or the compound ammonias. These are probably formed in the liver, or result there from the inability of the liver fully to convert ammonia salts into urea, the stimulus for which may be found in the intestinal walls. In addition to this the toxins may be formed by bacteria, such as the colon bacillus. The antitoxins may be greatly developed by proper training. Hard work produces fatigue toxins, and these in turn lead to the development of the antibodies. "I do not mean that it is right to assume that in nervous Americans worry produces fatigue, but it would almost seem so from the fact that they very commonly say, 'You make me tired,' instead of saying, 'you trouble' or 'you worry me.' One of the curious things about emotional fatigue is the rapidity with which it comes on, and this may possibly be explained by the fact that Weichardt found that the gray substance of the brain yields a fatigue toxin of great power." Cardiac dilatation is especially liable to occur in rapidly growing children, and is often the cause of the tired feeling of which they complain. This is one of the reasons why systematic physical

training should not be developed in the schools save under competent medical supervision. When the training is properly graded not only do the muscles become stronger and less easily fatigued, but the heart acquires additional strength. The famous wrestler Milo, of Crotona, carried a newly born calf day by day until it developed into a fully grown bull. Muscular training may help us to bear even that form of fatigue that comes from worry and mental depression. "Among all games, those of ball have been favorites, and they not only give pleasure and exercise to the muscles, but they tend to increase the power of coördination, which is of much more value than simple muscular power." There is a painting on an Egyptian tomb about 3500 years old, showing ladies tossing balls. "A very interesting problem may yet turn out to be the relationship between intestinal toxemia and the statement which has been put into the mouth of the unemployable British workman: 'I eats well, I drinks well, I sleeps well, but when I see a job of work coming along, I'm all of a tremble.'"

Health in the Tropics.—CHARLES (*Practitioner*, lxxxiv, 13) gives his experience in preserving the health of his family in India. Only boiled water should be used. Meat must come to the table straight from the fire. Alcohol is wholly unnecessary. Only those fruits that possess a rind that can be stripped off clean should be eaten. This excludes grapes, but permits oranges, banannas, apples, and pears. A filter should not be used, for its care is sure to be neglected. Clothing must be regulated by the temperature of the day and not by the season of the year. The "Kummerband," or abdominal binder of flannel, is not needed by a healthy man. Perfect cleanliness and the use of carbolic soap are the best prophylactics for the dhobie itch. Even in the hottest weather a light blanket should be provided, for about 3 A.M. there is a sudden fall in the temperature. Low shoes permit the mosquitos to bite the ankles, and top boots should be worn. Quinine and nets are necessary. When a man begins to worry he should leave the tropics, and only those in good health should go there. The Government gives one year's leave in five, and the Government would not do this had it not been found necessary.

Notice to Contributors.—All communications intended for insertion in the Original Department of this JOURNAL are received only *with the distinct understanding that they are contributed exclusively to this* JOURNAL.

Contributions from abroad written in a foreign language, if on examination they are found desirable for this JOURNAL, will be translated at its expense.

A limited number of reprints in pamphlet form, if desired, will be furnished to authors, *provided the request for them be written on the manuscript.*

All communications should be addressed to—

DR. A. O. J. KELLY, 1911 Pine Street, Philadelphia, U. S. A.

INDEX.

A

Abbott, Principles of Bacteriology, 280
Abdominal myomectomy for large uterine fibroids, 920
palpatory albuminuria, 128
surgery, mortality rate in, 773
prevention of adhesions in, 460
Acetone-alcohol for the disinfection of the field of operation, 445
Acoin, 152
Acoustic nerve, tumors of, 551
Actinomycotic cerebrospinal meningitis, 288
Adami, Principles of Pathology, 745
Adams, S. S., typhoid fever in children, 638
Adams-Stokes disease with complete heart block, 62
syndrome, 503
Addison's disease, acute, 127
Adenoid hypertrophy and its treatment, 300
vegetations, ablation of, 463
Adiposis dolorosa with myxœdematous manifestations, 359
Adrenalin in pernicious nausea of pregnancy, 615
Air of the operation room as a possible factor in the infection of wounds, 921
Albumin in urine, new tests for, 128
Albuminuria, abdominal palpatory, 128
Albuminuric coryza, 463
Albuminous substances in urine, detection of, 154
Allan, J., treatment of chorea in children, 165
Allbutt, System of Medicine, 274
Aluminum silicate in treatment of gastric disease, 765
Amenorrhœa, stem pessary for, 620
Amœbic dysentery in canal zone, 287
Anæmia pseudoleukæmica infantum, relationship of, to rachitis, 284
Anaphylaxis, immediate reaction of, 755
Anemia, pernicious, 611
Anemias, human blood transfusion in treatment of severe, 451
Anders, J., M., congenital single kidney 313
Angioneurotic œdema, 612
Antidiphtheritic sera, injections of, 907
serum and antidiphtheritic globulin solutions, 764
intravenous injections of, 296
Antitrypsin in blood serum and its mode of action, nature of, 778
Antitryptic activity of human blood serum, 714
Arterial hypertension, 648
Aortic insufficiency, association of, with syphilitic aortitis, 597
Aortitis, chronic, 311
Appendicitis, etiology of, 602
Arterial hypertension of labyrinth, 308
Arteriosclerosis and palpable thickening of the arterial wall, 439
cause of, 779
of pulmonary artery, 132
Aronson, E. A., gastric secretion, 233
Arthritis, dry, treatment of, with injections of vaseline, 911
Artificial anemia in intracranial operations, 290
reproduction of the amniotic liquid during labor, 772
Aseptic purulent meningeal exudates, 131
Ashton, Practice of Gynecology, 433
Asphyxia of extremities, local, 238
Asthenopia, nervous, 777
Atlo-axoid fracture dislocation, 758
Atresia of vagina with hematometra, hematosalpinx, and hematovarium, 149
Auricular fibrillation, 754
Auriculonodal junction, 287

B

Bacon, Manual of Otology, 125
Bacteria of stools in cancer of stomach 443
Bacterial vaccines, therapeutic use of, 39
Bandler, Medical Gynecology, 901
Balfour, Third Report of the Welcome Research Laboratories at the Gordon Memorial College, Kartoum, 899
Ballenger, Diseases of the Nose, Throat, and Ear, 434

Bangs, L. B., treatment of gonorrhœa, 664
Barker, L. F., paroxysmal arteriospasm with hpyertension in the gastric crises of tabes, 631
Bartholin, gland of, tuberculosis of, 306
Beri-beri, etiology of, 754
Biceps of arm, rupture of, 133
Bier's passive congestion, 177
Bile acids as a cathartic, 601
Billings, F., vaccine therapy in colon-bacillus infection of urinary tract, 625
Bishop, L. F., Adams-Stokes disease with complete heart block, showing a conspicuous lesion in the path of the auriculoventricular bundle, 62
Blackburn, Illustrations of the Gross Morbid Anatomy of the Brain in the Insane, 126
Blepharospasm and spastic entropion, injections of alcohol in, 777
Blood findings in pulmonary tuberculosis, 905
pressure, lowering of, by the nitrite group, 297
raising substance of kidney, 310
protozoa in, 312
regeneration from diminished oxygen tension, 286
in rickets, 917
Bone and joint tuberculosis, treatment of, 762
sarcoma, 137
Bonney, C. W., inguinal hernia, 188
Breast, benign diseases of, 759
removal of, for cancer, 289
Brill, N. E., acute infectious disease of unknown origin, 484
Bromine preparation in treatment of epilepsy, 452
Buerger, L., is thrombo-angiitis obliterans related to Raynaud's disease and erythromelalgia?, 105
Burton-Fanning, Open-air Treatment of Pulmonary Tuberculosis, 591
Burvill-Holmes, E., alleged presence of tubercle bacilli in the circulating blood, 99

C

Cabot, Physical Diagnosis, 281
Calcium lactate in hemorrhages of upper air tract, 610
Calculi, ureteral, 606
Calkins, Protozoölogy, 120
Camp, C. D., syphilitic paralysis of the trigeminal nerve, 402
Camphor and pneumococci, 451
Canal zone, amœbic dysentery in, 287
Cancer in mice, effect of trypsin on, 443
of cervix uteri, 306
Cancer of intestines, diagnosis of, 211
of stomach, 284, 443
of uterus, 148
removal of breast for, 289
Carbohydrates, utilization of, 422
Carcinoma, cervical, operation for, 462
skin reaction in, 264
Cardiac death, 518
stasis on the distribution of blood to the internal organs, 440
Cardiolysis, 444
Cathartic drugs in children, effect of, 454
Catheterization, retrograde, 910
Celiotomy, after-treatment of, 305
Cellulose and hemicellulose digestion in man, process of, 139
Cerebral hemorrhage in a child, 613
Cerebrospinal meningitis, 917
epidemic, serum therapy of, 295
Cervical rib, 108, 469
Cervix, dilatation of, local anesthesia in, 307
methods of operation in, 302
uteri, laceration of, 145
Cesarean section, suprasymphyseal, 303, 304
Chapin, Theory and Practice of Infant Feeding, 435
Cheney, W. F., diagnosis of cancer of intestines, 211
Chetwood, C. H., suprapubic prostatectomies, 72
Chicken leukemia, inoculations of, 441
Chloral hydrate as a local application, 766
Chorea in chidlren, treatment of, 165
Chromaffin system in cases of unexplained postoperative death, changes in, 780
Cleft palate, 612
Coal tar in treatment of diseases of skin, 621
Cohen, S. S., essential pentosuria, 349
Collum, Practice of Anesthetics, 435
Colostrum, unusual persistence in secretion of, 767
Compressed-air illness, etiological factors of, 373
Compression of superior mesenteric artery upon the systemic blood pressure, 180
Congenical single kidney, 313
Cooper, C. M., routine examination of œsophagus, 221
Cranial nerves in tabes dorsalis, 406
Creatinine and creatine, 256
Cushing, H., functions of the pituitary body, 473
Cyclic or recurrent vomiting with hypertrophic stenosis of pylorus, 768
Cystitis, treatment of, 759

Cystitis with incomplete retention of urine, 446
Cystocele and uterine prolapse, operative treatment of, 148

D

Da Costa, Principles and Practice of Physical Diagnosis, 122
Death, causes of sudden, 443
Deaver, J. B., use and abuse of gastro-enterostomy, 655
Decompression in treatment of meningitis, 344
Deficient dilatation of cervix, methods of operation in, 302
Delirium tremens, veronal in, 441
Dench, C. B., treatment of acute otitic meningitis, 157
Dermatitis herpetiformis, 621
Dermatoses, itching, 621
Determination of urinary ammonia and acidity, 906
Dextrose consumption by the heart, 597
Diabetes, influence of different carbohydrates upon the glycosuria in, 140
insipidus, dietetic treatmentof, 914
mellitus, atropine sulphate and atropine methylbromide in, 138
febrile diseases in, 286
mellitus, energy requirement in, 914
treatment of, 915
Dietary of goutily disposed persons, 915
Digitalis, effect of, 753
substitutes for, 766
Dilated renal pelvis, diagnosis of, by means of filling it with a colloid silver solution and skiagraphy, 291
Divulsion, value of, 134
Duodenum, resection of middle portion of, 135
Dwarf tapeworm, 769
Dysmenorrhœa and sterility in women, operation for, 617
stem pessary for, 620

E

Ear, noma of, 301
Earnshaw, H. C., Adams-Stokes syndrome of prolonged duration, 303
Eczema, trade, 621
Egyptian girls, age of menstruation in, 774
Ehrlich, Experimental Researches on Specific Therapeutics, 432
Electric caustic snare, 464
Elliott, A. R., arterial hypertension, 648
Elsberg, C. A., skin reaction in carcinoma from the subcutaneous injection of human red blood cells, 264
Emery, Immunity and Specific Therapy, 432
Endometrium and some of its variations, 773
Enterectomy under spinal anesthesia, 613
Epilepsy, 417
operative treatment of, 605
treatment of, 452
Epithelioma of larynx, 464
of uterus after menopause, 148
Erythromelalgia, 105
Eucalyptus in treatment of pertussis, 298
Ewing, J., pathogenesis of the toxemia of pregnancy, 828
Experimental acute nephritis, 806

F

Facial nerve, resistance capacity of, 309
Fallopian tube, occlusion of, 618
Fat percentages in infant feeding, regulation of, 916
Fats in treatment of disorders of stomach, 440
Febrile diseases in diabetes mellitus, effect of, 286
Feeding of immature and atrophic infants, 301
Fibromas of uterus, 461
Flail-like rib, 108
Flatulence and its treatment, 916
Flexner and Jobbling's anti-serum in cerebrospinal meningitis, 455
Flexner's serum for cerebrospinal meningitis, 917
Flora, normal, of rabbit's conjunctiva, 152
Fœtal membranes, rupture of, 145
rickets, 143
Foote, E. M., solitary false neuroma, 884
Fox, H., Wassermann and Noguchi complement-fixation test in leprosy, 725
Francine, A. P., cervical rib, 108
effect of tuberculosis on intrathoracic relations, 732
Freud, Hysteria and Other Psychoneuroses, 430
Friedman, G. A., local asphyxia of extremities, 238
Frontal sinus, malignant growths of, 153
Furunculosis and acute pemphigus neonatorum, 42

G

Garceau, Tumors of Kidney, 593
Gastric crises of tabes, 631
disease, treatment of, 765
juice, secretion of, in pathogenesis and course of pyloric stenosis of nursing infants, 300
lavage, 790
secretion, 233
use of fats in, 453
ulcer, iron chloride gelatin in treatment of, 453
treatment of, 140, 294
hemorrhage from, 790
Gastro-enterostomy, use and abuse of, 655
Gastro-intestinal diseases of infancy, urine in, 456
Gastroptosis, treatment of, 765
Geist, S. H., skin reaction in carcinoma from the subcutaneous injection of human red blood cells, 264
Gibson, C. L., technique of operations on the lower portion of the ureter, 65
Glandular fever, 142
Glioma of spinal cord, 143
Glycuronic acid in urine in health and disease, quantity of, 756
Gonorrhœa, treatment of, 664
Gout, treatment of, 915
Griffin, W. A., chronic family jaundice, 847
Gynecological massage, new kind of, 462

H

Haberman, J. V., myatonia congenita, of Oppenheim, 383
Hare, Practical Therapeutics, 902
Progressive Medicine, 431
Harvard, Manual of Military Hygiene for the Military Services of the United States, 437
Health in tropics, 926
Heard, J. D., cardiac death, 518
Heart-block, clinical observations in, 246
massage in surgery, 137
muscle, influence of coronary disease on, 311
surgery of, 133
Helmholt's theory of accomodation, 777
Helminthiasis in children, 675
Hemolysin method in diagnosis of cancer of stomach, 623
Hemolysis in cancer, significance of, 444
Hemolytic jaundice, 624
Hemophilia, 363
neonatorum, 800
Hemoptysis of phthisis and its treatment, 450
Hemorrhage from gastric ulcer, treatment of, 790
of spleen, treatment of, 581
Hemorrhagic disease in newborn with direct transfusion, 142
uteri, 920
Hemostasis in operations on skull, 909
Henoch's purpura, 612
Herbert, Cataract Extraction, 751
Hernia, inguinal, 188
of ureter, 289
operation for non-incarcerated, 604
Herrick, W. W., clinical observations in heart-block, 246
High caloric diet in typhoid fever, 27
Hirschman, Diseases of Rectum, 592
Hirst, Text-book of Obstetrics, 902
Hoobler, B. R., therapeutic use of bacterial vaccines, 39
Hort, Rational Immunization in the Treatment of Pulmonary Tuberculosis, 594
Houghton, H. A., high caloric diet in typhoid fever, 27
Hultgen, J. F., decompression in treatment of meningitis, 344
Hunter, Severest Anemias, 427
Hyde, J. N., pellagra and some of its problems, 1
Hydrarthrosis, 599
Hydrocephalus, treatment of, 910
Hyperemia, passive, therapeutic use of, 177
Hyperthyroidism, ligation of thyroid vessels in cases of, 447
Hypogastric retrograde catheterization, 910
Hysterectomy, early, 148
subtotal, 306

I

Increased secretion of intestines in dogs, 293
Infant feeding, regulation of fat percentages in, 916
Infantile diarrhœas, treatment with lactic acid bacilli of, 299
paralysis, 756
scorbutus, 919
Infectious disease, acute, 484
Influence of corsets and high-heeled shoes on the symptoms of pelvic and static disorders, 307
Influenzal septicemia, 527
Inguinal hernia, 188
Inner pole magnet, 153
Inoculations of chicken leukemia, 441
Intermittent achylia gastrica, 238
hydrarthrosis, 599
Internal rotation in labor, factors producing, 456
urethrotomy, value of, 134

Interruption of pregnancy for pulmonary tuberculosis, 303
Intestinal fermentation, 299
indigestion in children, treatment of, 781
obstruction in children, 912
Intestines, cancer of, diagnosis of, 211
Intrahuman bone grafting and reimplantation of bone, 446
Intraperitoneal and extraperitoneal ureterolithotomy for removal of stones from lower ureter, 921
Intravenous injections of antidiphtheritic serum, 296
narcosis, 908
Intraventricular injection of Flexner's serum for cerebrospinal meningitis, 917
Itching dermatoses, treatment of, 621

J

JAUNDICE, chronic family, 847
hemolytic, 624
in pneumonia, 756

K

KAPLAN, D. M., principles and technique of the Wasserman and Noguchi reactions, 82
Kaufmann, J., treatment of hemorrhage from gastric ulcer, 790
Kerley, Short Talks with Young Mothers on the Management of Infants and Young Children, 596
Kidney, blood-pressure-raising of, 310
single, 313
Kimber, Anatomy and Physiology for Nurses, 588
Knight, Diseases of the Nose, Throat, and Ear, 594
Knopf, Tuberculosis, 124
Krause, Clinical Diagnosis of Internal Disease, 750

L

LA WALL, C. H., urine containing pentose, 357
Labyrinth, arterial hypertension of, 306
Lacerations of cervix uteri, 145
Lacunar tonsillitis, acute, 464
Larned, C. W., hemophilia, 363
Larynx, morbid growth of, 464
Lavage, gastric, 790
Leprosy, 725
Leukocytic extract in treatment of pneumonia, 131
Liebe, Vorlesungen über Tuberkulose, 280
Long, Physiological Chemistry, 749
Lucas-Championnière, Pratique de la Chirurgie Antiseptique, 278
Lungs and trauma, 601
wounds of, 760
Lupus or tertiary syphilis, 620
Lysol poisoning from irrigation of uterus during suprasymphyseal Cesarean section, 303

M

McCAMPBELL, E. F., acute pneumococcic meningitis, 536
McWharter, J. E., compressed-air illness, 373
Madison, J. D., influenzal septicemia, 527
Magnesium poisoning, 609
Magnet extractions, report on, 776
Malignant growths of frontal sinus, 153
Mammary glands, abnormal secretion from, 306
Martin, Surgical Diagnosis, 272
Massage, heart, in surgery, 137
McIsaac, Elements of Hygiene for Schools, 587
Hygiene for Nurses, 588
Bacteriology for Nurses, 588
McKenzie, Exercise in Education and Medicine, 115
Meara, F. S., treatment of rheumatic fever, 328
Mendel, L. B., physiological utilization of some complex carbohydrates, 422
Meningitis, decompression in treatment of, 344
Mercury, action of, 600
Middle-ear disease, conservative treatment of, 921
Milk, dried, as a food for infants, 767
Minot, The Problem of Age, Growth, and Death, 118
Mitral insufficiency, experimental functional, 286
Monochord and the upper tone limit, 308
Montgomery, C. M., murmurs in pulmonary tuberculosis, 870
Moore, History of the Study of Medicine in the British Isles, 124
Morse, J. L., treatment of intestinal indigestion in children on the basis of the examination of the stools and caloric values, 781
Müller, G. P., therapeutic use of passive hyperemia, 177
Murmurs in pulmonary tuberculosis, 870
Muscle bundle between the superior vena cava and the His bundle, 129
Musculospiral paralysis complicating fracture of humerus, 447
Myasthenia gravis, metabolism of, 816

Myatonia congenita, of Oppenheim, 383
Myers, V. C., physiology and pathology of creatinine and creatine, 256
Myoma uteri, fever in, 619
Myomectomy, abdominal, 920
Myopathic uterine hemorrhage, 920
Myopia and light sense, 776

N

Nail-palpation of arterial wall, 757
Narcosis, intravenous, 908
Necrosis of fibromyoma of gravid uterus as an etiological factor in occlusion of intestinal tract, 149
Nephritis, acute, 806
Neuhof, H., epidemic of noma, 705
skin reaction in carcinoma from the subcutaneous injection of human red blood cells, 264
Neuroma, solitary false, 884
Nickel utensils, 925
Nitrite group, lowering of blood pressure by, 297
Noma, epidemic of, 705
of ear, 301
Normal human blood serum as a curative agent in hemophilic neonatorum, 800

O

Obesity, treatment of, 141
Obstruction of bowels, 293
Œdema, acute pulmonary, 417, 766
Œsophagus, routine examination of, 221
Ohlmacher, A. P., acute pulmonary œdema as a terminal event in certain forms of epilepsy, 417
Operations on skull, 909
Optic atrophy from use of atoxyl and arsacetin, 140
Orthopedic operations, convulsions following, 605
Osler, W., certain vasomotor, sensory, and muscular phenomena associated with cervical rib, 469
Osteomas, of tracheal mucous membrane, 464
Otitic meningitis, acute, treatment of, 157
Otosclerosis, 922
Ovarian abscess containing a lumbricoid worm, 772
cyst with twisted pedicle complicating pregnancy, 771
displacements, 461
papillary adenocarcinoma, 462
tumor, removal of, 774
Ovariotomy, later results of, 920
Ovariotomy and myomectomy early in pregnancy, 771
Ozena, paraffin injections in, 463

P

Paralysis, infantile, 756
Paratyphoid fever, epidemic of, 598
Paroxysmal arteriospasm with hypertension in the gastric crises of tabes, 631
Pathogenesis of toxemia of pregnancy, 828
Pellagra and some of its problems, 1
Pelvic and static disorders, influence of corsets and high-heeled shoes on symptoms of, 307
Pelvis, operation for a chronic inflammatory mass in, 619
Pemberton, R., metabolism of myasthenia gravis, 816
Pentose, urine containing, 357
Pentosuria, essential, 349
Peptid-splitting ferment in cancer of stomach, 284
Pernicious anemia, 611
pathogenesis of, 154
nausea of pregnancy, adrenalin in, 615
Peripheral sensation during pregnancy, 771
Peritoneal adhesions, significance of, 306
Peritonitis, acute diffuse, 919
Pertussis, treatment of, with eucalyptus, 298
Phenoltetrachlorphthalein, 608
Physiological saline solution, infusion of, 909
Pituitary body, function of, 473
Pneumococcic meningitis, acute, 536
Pneumonia, 756
action of leukocytic extracts on course of, 662
treatment of, by leukocytic extract, 131
Poliomyelitis, acute, 769
anterior, 611
experimental, transmission of, 132
Polyhydramnios complicated with œdema, 457
Postoperative peritoneal adhesions, 150
Pregnancy complicated by nephrectomy and ovariotomy, 458
occurring after operations for correction of retroflexion, results of, 772
toxemia of, 828
Proctosigmoiditis, treatment of, 911
Prolapse of uterus, 618
Prostatectomies, suprapubic, 72
Protozoa in blood in typhus fever, 312

Pseudomeningococci in throats of healthy children, 925
Puerperal period, position of patient during, 147
sepsis, surgical treatment of, 616
septic infection, 770
Pulmonary tuberculosis, 905
murmurs in, 708
Purgatives, subcutaneous, 608
Purpura hæmorrhagica due to benzol poisoning, 598
Henoch's, 612
Pyosalpinx, spontaneous rupture of, 919

Q

Quantitative determination of caloric nystagmus in the normal labyrinth, 922
index to tuberculin treatment, 130

R

Rachitis, use of phosphorus in, 141
Rat-bite fever, 757
Raynaud's disease, 105, 238
Refractive anomalies and emmetropia, etiology of, 152
Resection of middle portion of duodenum, 135
Resection of posterior spinal roots, 822
Retention of pieces of placenta with the occurrence of fever, treatment of, 144
Retina, detachment of, 775
Retrodisplacement of uterus, 773
Retroflexio uteri, combination of Pfannenstiel's transverse incision and shortening of the round ligaments in operative treatment of, 148
Reviews—
Abbott, Principles of Bacteriology, 280
Adami, Principles of Pathology, 745
Allbutt, System of Medicine, 274
Ashton, Practice of Gynecology, 433
Bacon, Manual of Otology, 125
Balfour, Third Report of the Welcome Research Laboratories at the Gordon Memorial College, Kartoum, 899
Ballenger, Diseases of the Nose, Throat, and Ear, 434
Bandler, Medical Gynecology, 901
Blackburn, Illustrations of the Gross Morbid Anatomy of the Brain in the Insane, 126
Burton-Fanning, Open-air Treatment of Pulmonary Tuberculosis, 591
Cabot, Physical Diagnosis, 281
Reviews—
Calkins, Protozoölogy, 120
Chapin, Theory and Practice of Infant Feeding, 435
Collum, Practice of Anesthetics, 435
Da Costa, Principles and Practice of Physical Diagnosis, 122
Ehrlich, Experimental Researches on Specific Therapeutics, 432
Emery, Immunity and Specific Therapy, 432
Freud, Hysteria and Other Psychoneuroses, 430
Garceau, Tumors of Kidney, 593
Hare, Practical Therapeutics, 902
Progressive Medicine, 434, 900
Harvard, Manual of Military Hygiene for the Military Services of the United States, 437
Herbert, Cataract Extraction, 751
Hirschman, Diseases of Rectum, 592
Hirst, Text-book of Obstetrics, 902
Hort, Rational Immunization in the Treatment of Pulmonary Tuberculosis, 594
Hunter, Severest Anemias, 427
Kerley, Short Talks with Young Mothers on the Management of Infants and Young Children, 596
Kimber, Anatomy and Physiology for Nurses, 588
Knight, Diseases of the Nose, Throat, and Ear, 594
Knopf, Tuberculosis, 124
Krause, Clinical Diagnosis of Internal Disease, 750
Liebe, Vorlesungen über Tuberkulose, 280
Long, Physiological Chemistry, 749
Lucas-Championnière, Pratique de la Chirurgie Antiseptique, 278
McIsaac, Elements of Hygiene for Schools, 587
Hygiene for Nurses, 588
Bacteriology for Nurses, 588
McKenzie, Exercise in Education and Medicine, 115
Martin, Surgical Diagnosis, 272
Minot, The Problem of Age, Growth, and Death, 118
Moore, History of the Study of Medicine in the British Isles, 124
Ritchie, Human Physiology, 590
Seward, Darwin and Modern Science, 428
Schultze, Atlas und Grundriss der Topographischen und Angewandten Anatomie, 437
Sinclair, Semmelweis, 586
Simon, Manual of Chemistry, 592

Reviews—
Snow, Therapeutics of Radiant Light and Heat and Convective Heat, 282
Soddy, Interpretation of Radium, 904
Starr, Organic and Functional Nervous Diseases, 903
Stewart, Practical Gynecology, 589
Thompson, Practical Dietetics, 438
William, Manual of Bacteriology, 436
Wilson, Medical Diagnosis, 897
Winter, Text-book of Gynecological Diagnosis, 276
Wharton, Minor and Operative Surgery, 433
Wood, Chemical and Microscopical Diagnosis, 750
Yearsley, Diseases of the Ear, 752
Rheumatic fever, treatment of, 328
Rhinopharyngeal fibroma fatal by intracranial extension, 465
Rhinopharyngocele, 463
Rickets, blood in, 917
Rickets, fœtal, 143
Ritchie, Human Physiology, 590
Rodman, W. L., inguinal hernia, 188
Rowland, G. A., acute pneumococcic meningitis, 536
Rupture of biceps of arm, 133
of fœtal membranes, 145

S

Saline solution, pure, 909
Salomon's test in diagnosis of cancer of stomach, 623
Sarcoma, bone, 137
of extremities, 293
or primary syphilis, 620
Schloss, O. M., helminthiasis in children, 675
Schultze, Atlas und Grundriss der Topographischen und Angewandten Anatomie, 437
Scorbutus, infantile, 919
Secretory gastric stimulants, experiments on, 599
Septicemia, influenzal, 527
Serous meningitis in typhoid fever, 542
Serum injections on the eosinophiles and mastzellen in man and animals, effect of, 907
Serum therapy of epidemic cerebrospinal meningitis, 295
Seward, Darwin and Modern Science, 428
Sheldon, J. G., hemorrhage of spleen, 581
Shoulder, double traumatic dislocation of, 449
Sinclair, Semmelweis, 865
Simon, Manual of Chemistry, 592
Skin, disinfection of, with tincture of iodine, 601
metastases in cancer of uterus, 148
reaction in carcinoma from the subcutaneous injection of human red blood cells, 264
tuberculosis of, 620
Skull, operations on, 909
vault of, traumatic injuries of, 292
Snow, Therapeutics of Radiant Light and Heat and Convective Heat, 282
Soddy, Interpretation of Radium, 904
Sodium sulphite, poisonous effects of, 924
Solitary false neuroma, 884
Spasticity and athetosis, treatment of, 822
Spiller, W. G., syphilitic paralysis of the trigeminal nerve, 402
treatment of spasticity and athetosis by resection of the posterior spinal roots, 822
Spinal cord, glioma of, 143
Spine, fracture-dislocations of, 604
Spirochæta pallida in syphilitic eye lesions, 151
Spleen, hemorrhage of, 581
Sputum test, new, 283
Staining of moist preparations with azure-eosin, 129
Starr, M. A., Organic and Functional Nervous Diseases, 903
tumors of acoustic nerve, 551
Stasis hemorrhages resulting from compression of thorax and abdomen, 761
Stein, R., serous meningitis in typhoid fever and its treatment by lumbar puncture, 542
Stem pessary for amenorrhœa, 620
Sterility, stem pessary for, 620
Stern, H., adiposis dolorosa with myxœdematous manifestations, 359
Stewart, Practical Gynecology, 589
Stokes-Adams syndrome, treatment of, 454
Stomach, cancer of, 284, 443, 623
perforating ulcer of, 445
Stones in lower ureter, removal of, 921
Strabismus, treatment of, by operation upon non-squinting eye, 153
Strophanthin, action of, 609, 610
Suppurative conditions in the joint regions in infants and young children, 300
Suprapubic prostatectomies, 72
Suprasymphyseal Cesarean section, 303, 304
section for pelvis of moderate contraction, 459
Surgery of heart, 133

Swartz, M. D., physiological utilization of some complex carbohydrates, 422
Syphilis, lupus or tertiary, 620
sarcoma or primary, 620
Syphilitic paralysis of trigeminal nerve, 402

T

Tabes dorsalis, cranial nerves in, 406
gastric crises of, 631
Tachycardia, paroxysmal, 442
Talbot, F. B., treatment of intestinal indigestion in children on the basis of the examination of the stools and caloric values, 781
Tapeworm, dwarf, 769
Tardy infection following operations, etiology of, 776
Tetany, undescribed symptom of, 758
Thompson, Practical Dietetics, 438
Thrombo-angiitis obliterans, 105
Thrombophlebitis with peroneal neuritis and paralysis following supravaginal hysterectomy, 150
Thyroid gland, active substance of, 600
Tileston, W., chronic family jaundice, 847
Tired, on being, 925
Toxemia of pregnancy, 828
Trachoma in Abruzzi, Italy, 777
Traumatic coxa vara and valga, treatment of, 448
Trephining in traumatic injuries of vault of skull, 292
Trigeminal nerve, syphilitic paralysis of, 402
Tropics, health in, 926
Trypanosomiasis, investigations upon, 155
Tubal convulsions and the mechanism of tubal occlusion, anatomy of, 774
Tubercle bacilli in circulating blood, presence of, 99
Tuberculin diagnosis and treatment, principles of, 913
therapy, present status of, 51
treatment among dispensary patients, 296
quantitative index to, 130
of tuberculosis, 764
Tuberculosis, 465
bone and joint, treatment of, 762
of skin, 620
of gland of Bartholin, 306
pulmonary, 732, 905
interruption of pregnancy for, 303
murmurs in, 870
urogenital, 761
Tuberculous meningitis, 612
Tumors of acoustic nerve, 551
Typhlitis, acute primary, 603
Typhoid fever, diet in, 763
high caloric diet in, 27
in a hemophilic subject, 363
in children, 638
protozoa in blood in, 312
serous meningitis in, 542

U

Ulcer of foot, perforating, 603
Ununited fractures, operative treatment of, 135
Ureter, hernia of, 289
operations on the lower portion of, 65
Ureteral calculi, 606
fistulas as sequels of pelvic operations, 149
Ureterocele, 289
Uric acid, excretion of, in gouty subjects, 129
Urinary ammonia and acidity, determination of, 806
fistulas in women, 461
Urine, albumin, in, 128
containing pentose, 357
Urogenital tuberculosis, 761
Uterine adenomyomas to rectum, extension of, 619
carcinoma, treatment of, 460
fibroids, abdominal myomectomy for, 920
myomas, enuclation of, 774
red degeneration of, 147
Uterus, cancer of, 148
chronic inversion of, 618
fibromas of, 461
influence of a bloodless condition of, 614
prolapse of, suprapubic operation upon the pelvic floor for, 618
retrodisplacement of, 773
retroversion of, new method of shortening the round ligaments in, 150
rupture of, 458
Utilization of some complex carbohydrates, 422

V

Vaccine immunity, 924
and serumtherapy in children, 301
therapy, general principles of, 607
in colon-bacillus infection of urinary tract, 625
Vaseline in treatment of dry arthritis, 911
Vault of skull, traumatic injuries of, 292
Venous pulse under normal and pathological conditions, 778

Veronal in treatment of delirium tremens, 441
Volvulus of intestines as a disease of hungry men, 450
Voorsanger, W. C., present status of tuberculin therapy, 51

W

Wassermann and Noguchi complement-fixation test in leprosy, 725
reactions, technique of, 82
reaction, 600
Weil, R., antitryptic activity of human blood serum, 714
Welch, J. E., normal human blood serum as a curative agent in hemophilia neonatorum, 800
William, Manual of Bacteriology, 436
Williams, T. A., cranial nerves in tabes dorsalis, 406
Wilson, Medical Diagnosis, 897
Winter, Text-book of Gynecological Diagnosis, 276
Wharton, Minor and Operative Surgery, 433
Wood, Chemical and Microscopical Diagnosis, 750
Wounds of extremities threatening gangrene, treatment of, 136
of lungs, 760

X

X-rays in treatment of bone and joint tuberculosis, 762

Y

Yearsley, Diseases of the Ear, 752
Yellow glasses, use of, 777

GENERAL LIBRARY,
UNIV. OF MICH.
MAY 30 1910

VOL. CXXXIX, No. 6 JUNE, 1910

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

EDITED BY A. O. J. KELLY, M.D.

THE TREATMENT OF INTESTINAL INDIGESTION IN CHILDREN ON THE BASIS OF THE EXAMINATION OF THE STOOLS AND CALORIC VALUES. By JOHN LOVETT MORSE, A.M., M.D., and FRITZ B. TALBOT, M.D. 781

THE TREATMENT OF HEMORRHAGE FROM GASTRIC ULCER. By J. KAUFMANN, M.D. 790

NORMAL HUMAN BLOOD SERUM AS A CURATIVE AGENT IN HEMOPHILIA NEONATORUM. By JOHN EDGAR WELCH, M.D. 800

THE METABOLISM OF MYASTHENIA GRAVIS, WITH A SUGGESTION REGARDING TREATMENT. By RALPH PEMBERTON, M.D. 816

THE TREATMENT OF SPASTICITY AND ATHETOSIS BY RESECTION OF THE POSTERIOR SPINAL ROOTS. By WILLIAM G. SPILLER, M.D. 822

THE PATHOGENESIS OF THE TOXEMIA OF PREGNANCY. By JAMES EWING, M.D. 828

CHRONIC FAMILY JAUNDICE. By WILDER TILESTON, M.D., and WALTER A. GIFFEN, M.D. 847

A STUDY OF MURMURS IN PULMONARY TUBERCULOSIS. By CHARLES M. MONTGOMERY, M.D. 870

TWO CASES OF SOLITARY FALSE NEUROMA—PROBABLY NON-MALIGNANT. By EDWARD M. FOOTE, M.D. 884

PHILADELPHIA AND NEW YORK
LEA & FEBIGER

COPYRIGHT 1910, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, FIVE DOLLARS A YEAR, POSTPAID

ANNOUNCEMENTS

COMPLETE WORK **JUST READY**

MODERN MEDICINE

ITS THEORY AND PRACTICE

In original contributions by Eminent American and Foreign Authors

Edited by WILLIAM OSLER, M.D.

Regius Professor of Medicine in Oxford University, England; Honorary Professor of Medicine in Johns Hopkins University, Baltimore; formerly Professor in the University of Pennsylvania, Philadelphia, and in McGill University, Montreal

In seven octavo volumes of about 900 pages each, illustrated. Price per volume, cloth, $6.00 net; leather, $7.00, net; half morocco, $7.50, net. Subscriptions received only for the whole work. Prospectus on request

The publication of the seventh volume completes the greatest work on practical medicine ever offered to the profession. Dr. Osler's preëminent position has enabled him to secure articles from the leaders in every department. Their coöperation under a skillfully devised plan has resulted in the creation of a complete library of present-day medicine within the convenient compass of about 6,000 pages, adequately illustrated. Each volume is indexed, and the seventh contains a general index to the whole, so that the latest authoritative information on any point is immediately at command. For a work of such paramount value and usefulness a phenomenal demand was assured and it was therefore possible to fix a price low enough to meet the convenience of every practitioner who aims to qualify in full measure for his responsibilities.

New (6th) Edition **Just Ready** **Thoroughly Revised**

A PRACTICAL TREATISE ON

FRACTURES AND DISLOCATIONS

By LEWIS A. STIMSON, B. A., M. D.

Professor of Surgery in Cornell University Medical College, New York City

Octavo, 876 pages, with 361 engravings and 65 full-page plates. Cloth, $5.00, net

A new edition of a work universally recognized as first and final authority by the medical and legal professions of America as well as by the courts. It is unique in literature as covering two cognate classes of common and urgent injuries that every general practitioner and surgeon must be qualified to treat. For their proper management, as well as to avoid or defend lawsuits, which are peculiarly apt to arise in such cases, every medical man owes it to his patients and himself to command the latest and most authoritative knowledge, offered in this great work. Its wide acceptance is shown in the demand for repeated editions. The author has again revised it to date, including the rarest as well as the common injuries of both classes. He has presented the results of his own immense experience interwoven with knowledge derived from familiarity with American and foreign literature on these subjects, so that the work is cosmopolitan in scope. Fully illustrated.

PHILADELPHIA
706-8-10 SANSOM ST.

LEA & FEBIGER

NEW YORK
111 FIFTH AVENUE

A Vaginal Tampon of

Antiphlogistine

Trade Mark

WE find that the use of Antiphlogistine in vaginal tampons is a new thought to many a physician, but when he once learns of it, he wonders that he has not used it in that way before. In fact, Antiphlogistine makes the ideal tampon, for while its hygroscopic properties deplete the congested parts, its plastic nature affords the required support.

TECHNIQUE.—Place the requisite quantity of Antiphlogistine in the centre of a square of gauze, gather the edges up around the Antiphlogistine, bag-fashion, tie a string around the neck of the bag and insert through a speculum.

Wherever inflammation or congestion is a factor, Antiphlogistine is indicated and should always be applied warm and thick and covered with absorbent cotton.

THE DENVER CHEMICAL MFG. CO., New York

CELLASIN (Metabolic Ferment Derived from Fungi)

A dependable influencer of nutrition clinically efficient in malnutrition as is nothing else

Produces These Important Effects

IN EARLY TUBERCULOSIS

Unmistakably increases the blood count. Enables the system to metabolize carbohydrates and fats. Increases appetite and weight

Chemistry and Scientific Rationale on Request

MEAD JOHNSON & CO.

JERSEY CITY - - NEW JERSEY

THERAPEUTIC OBSTACLES

Overcome by Bayer Products

SAJODIN
Well-Tolerated Iodide

SABROMIN
Palatable and Active Bromide

NOVASPIRIN
Well-Borne Salicylate

THYRESOL
Santal Oil minus its Disadvantages

HELMITOL
Improved Hexamethylen-tetramin

SPIROSAL
Non-Irritating Local Salicylate

CORYFIN
Prolonged Acting Menthol

IOTHION
Local Iodin Absorbent

Samples and Literature Supplied by

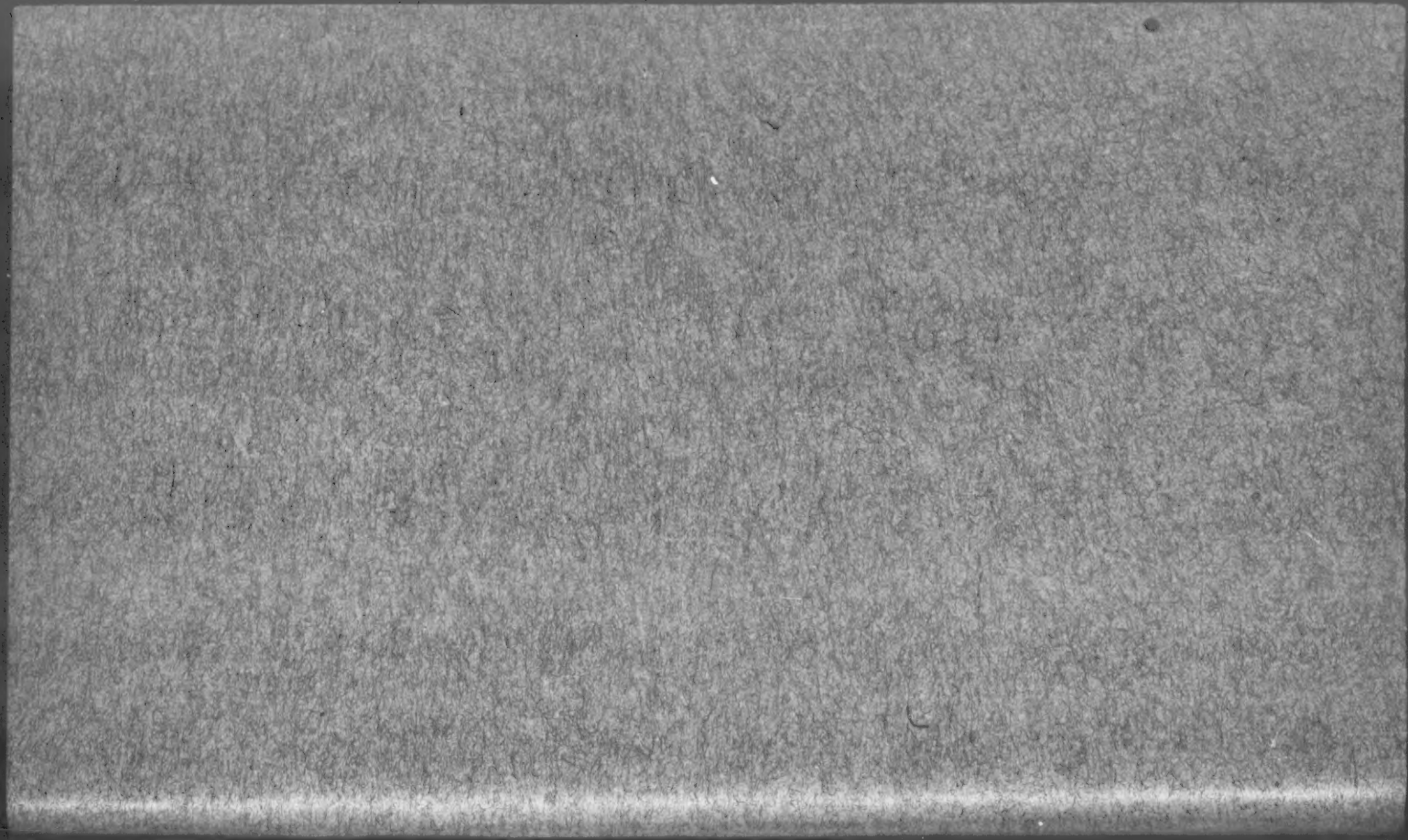
Farbenfabriken of Elberfeld Co.

P. O. BOX 2162 NEW YORK 117 HUDSON STREET

Mellin's Food

with fresh milk is the most effective and satisfactory method of infant feeding.

A great many physicians are using this method now with their own babies which is sufficient evidence of their confidence in its merits.

Trial bottles and literature are free to the medical profession on request.

Mellin's Food Company, Boston, Massachusetts.